HENRY FORD HOSPITAL MEDICAL BULLETIN

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INTIMATIONS RELATING TO PROTEIN FORMING DISEASES*

WILLIAM S. HAUBRICH, M.D.**

According to Webster, intimations are 'suggestions obscurely or indirectly made'. In this essay it is speculative suggestions, some obscure and some indirect, that I will attempt to relate to certain protein-forming diseases.

Increasing attention is being directed to the emergence of a group of disease states — of probably diverse etiologies, of diverse manifestations, and even of diverse courses — but which yet seems to share commonly the fact that each disease is constituted morphologically by the presence of ontogenetically similar cells which are capable of elaborating abnormal protein substances.

Because its clinical behavior and, particularly, its morphologic features have occupied our recent study[1], the condition which I submit as a prototype of these states is Whipple's disease.

HISTORICAL BACKGROUND

It is noteworthy that George H. Whipple, in his original report[2] of the disease for which his name is now the eponym, described in detail within the small intestine and mesentery a profusion of "peculiar cells with frothy cytoplasm" in addition to the more obvious anomalous accumulations of fats and fatty acids. It is these peculiar cells which we recognize now as the most significant feature of Whipple's disease.

The Henry Ford Hospital can claim an extraordinary share in the developing knowledge of Whipple's disease. Black-Schaffer, an alumnus of this hospital, provided a major breakthrough in 1949 by demonstrating the striking tinctorial response in tissue from Whipple's disease to the periodic acid-Schiff (PAS) technic[3]. Puite and Tesluk[4], both members of the staff of this hospital at the time of their 1955 report, established the diagnosis of Whipple's disease by peripheral lymph node biopsy. In 1958 Sieracki, until recently associated with this hospital's department of laboratories, directed attention to the unusual configuration of the cytoplasmic inclusions in the "frothy cells" and coined the term "sickle-form particle containing" (SPC) cells[5]. Sieracki and Fine[6] then catalogued the occurrence of these SPC cells in tissues representing all major anatomic systems thus confirming that Whipple's disease is a widespread, systemic affection. Involvement of the central nervous system was the subject of a special report by Sieracki, Fine, Horn, and Bebin[7]. Meanwhile, Eyler and Doub[8] described the extraintestinal roentgen signs of Whipple's disease. It was in the physics department at the Edsel B. Ford Institute for Medical Research that the ultrastructure of the SPC cells and their cytoplasmic inclusions was first demonstrated by electron microscopy[1].

THE SPC CELLS

The characteristic cell of Whipple's disease is a large (average diameter: 20μ to 30μ), usually mononuclear cell. By the ordinary hematoxylin-and-eosin technic,

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*Abridged from an address to the Henry Ford Hospital Medical Society, April 6, 1961.
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the cytoplasm of these cells appears "frothy" because of numerous slightly basophilic particles faintly visible against a lightly eosinophilic background. In the cytoplasm of an occasional cell, a few droplets of fat may be seen, but the great bulk of the material is nonsudanophilic. The nucleus is relatively small, unilobular, and eccentric.

After treatment by the PAS technic, the intracytoplasmic particulate substance appears as a brilliant magenta (PAS-positivity). There is no doubt that the "peculiar cells with frothy cytoplasm" mentioned by Whipple[2] are identical with the SPC cells described by Sieracki[5]. This was proved when Mendeloff[9] applied the PAS technic to tissue preserved from Whipple's original case and demonstrated precisely the tinctorial reaction and the morphologic configuration which we recognize as pathognomonic today.

Within the peculiar cells of Whipple's disease, the PAS-positive material occurs as sickle-form particles (averaging 2μ to 3μ) of varying density and also as amorphous clumps and strands (Figure 1). The true sickle-form configuration of these particles is best appreciated in imprints rather than in ordinary tissue sections. In imprints the particles are seen in their entirety rather than as random transverse or oblique sections. All solid tissues lend themselves to the imprint technic which we have found especially useful in applying to biopsies from peripheral lymph nodes and from the small intestine mucosa in Whipple's disease.

It is emphasized that PAS-positivity by itself does not confer distinction on the substance peculiar to Whipple's disease. A variety of glycoproteins or mucopolysaccharides react tinctorially with the PAS technic. In the normal intestinal mucosa, for example, PAS-positivity is exhibited by mucus adherent to the free border of the intestinal epithelial cell, by mucoid substance in goblet cells, and by faint strands of mucoid material in the lamina propria. It is the particulate configuration of the PAS-positive substance in abundant cells abnormally situated in the lamina propria which is unique in Whipple's disease.

Anatomic Occurrence of SPC Cells. Characteristic SPC cells invariably occur both in mesenteric and in peripheral lymph nodes. The latter provides a readily accessible site for biopsy, and this procedure has provided the diagnosis of Whipple's disease in 3 patients of our own series.

Equally abundant are the SPC cells in the lamina propria of the small intestine, but they are regularly found in all other segments of the gastrointestinal tract including the esophagus, stomach, and colon. With the newly developed technics for peroral biopsy of the small intestine mucosa, a diagnosis of Whipple's disease is promptly confirmed by the imprint technic (Figure 1) which we have successfully applied in 3 cases.

In the liver, SPC cells occur both in the portal and subendothelial spaces. It is noteworthy that the liver architecture is not distorted and, as in most other situations, there is no appreciable inflammatory reaction adjacent to collections of SPC cells.

In the spleen, SPC cells are distinct from morphologically similar cells containing only iron pigment. This suggests that SPC cells do not represent the ordinary tribe of macrophages which may perform only a simple phagocytic function.

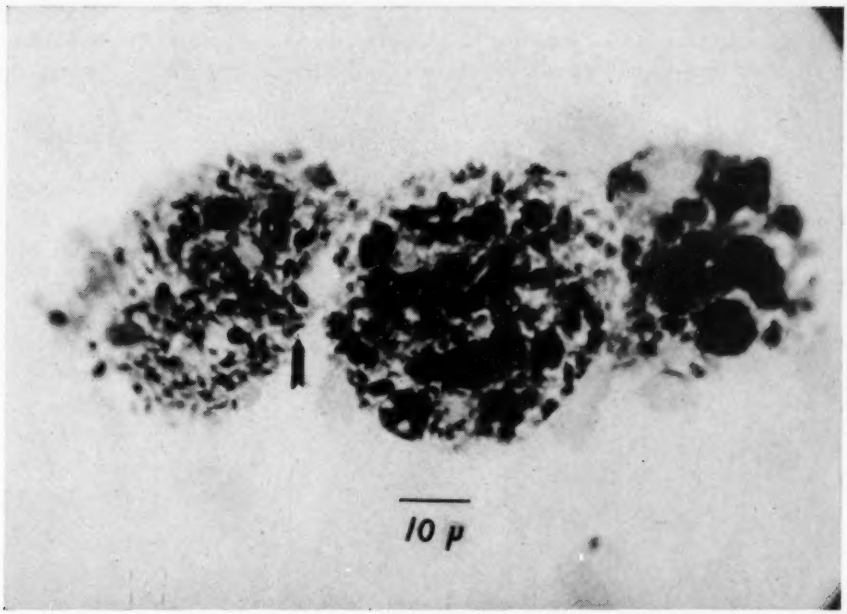

Figure 1

Three SPC cells aligned in an imprint from a peroral jejunal mucosa biopsy. The PAS-positive inclusions, actually a brilliant magenta, appear black in this reproduction. Arrow indicates a typical sickle-form particle in the cell at left. Larger, denser, amorphous clumps appear in cells at center and right. Periodic acid-Schiff, 1320x.

Clusters of SPC cells may occupy the connective tissues of the heart valves, the epicardium, and the myocardium. Endocardial vegetations, occasionally observed in Whipple's disease, are made up, in part, of agglomerations of SPC cells.

It is significant that, in the lung, SPC cells occupy the positions of the so-called "septal cells" which are histiocytes representing the reticulo-endothelial system in the interalveolar septa (Figure 2). SPC cells commonly are found in the pleura.

Surprisingly abundant are collections of SPC cells in the central nervous system where they occur as ependymal nodules and scattered in the glial tissues.

Anatomic evident recently compiled[1,6] strongly supports the contentions that Whipple's disease is a widespread, multiple system disease.

Derivation of the SPC Cell. The ubiquity of the characteristic SPC cells of Whipple's disease suggests that they are derived from cellular elements normally present in tissues throughout the body. The alternative explanation by metastasis seems unlikely because the anatomic distribution of SPC cells fits neither that of lymphatic nor of hematogenous spread from a single focus.

The elemental cell system which includes all of the sites in which SPC cells have been identified is the reticulo-endothelial system. We suggest, in a manner of

speaking, that the forefather of the SPC cell is the reticulo-endothelial stem cell, that its cousins are plasma cells and lymphocytes, and that its better known siblings go by the names of histiocytes, macrophages, and clasmatocytes, among others.

Figure 2

SPC cells (*arrows*) occupying the interalveolar septa of lung in Whipple's disease. Periodic acid-Schiff, 250x.

THE PAS-POSITIVE SUBSTANCE

In electron micrographs of SPC cells, the intracytoplasmic inclusions, which correspond to those reacting to the PAS technic at light microscopy, appear in 2 forms (Figure 3). The sickle-form particles are readily identified by their commensurate size and shape. Where by light microscopy these particles appear homogeneous, by electron microscopy they are seen to be made up of clusters of minute vesicles or labyrinthine networks surrounded by limiting linear densities or "membranes". The inclusions which appear as amorphous clumps or strands of PAS-positive material by light microscopy are seen in electron micrographs as innumerable, densely packed, minute, cylindrical bodies. The cores of these minute bodies appear relatively clear, *i.e.*, they exhibit little affinity for the osmium fixative, while their shells are dense and, hence, osmiphilic. Each cylindrical body is surrounded by a fine membrane. These observations, first made in this laboratory, have been subsequently confirmed by Cohen and his co-workers at the Massachusetts General Hospital[10].

It is our supposition that the clusters of vesicles or reticula within the sickle-form particles represent the sites of synthesis of a protein-carbohydrate complex which then assumes the form of the densely packed, cylindrical bodies. This supposition implies that the PAS-positive substance of Whipple's disease occurs within the cells, not as a result of phagocytosis as generally believed, but rather that this substance is formed within the cytoplasm of the cells themselves.

The idea of proteinaceous elaboration by the peculiar cells of Whipple's disease was first conceived as a result of histochemical observations. In studies of the PAS-

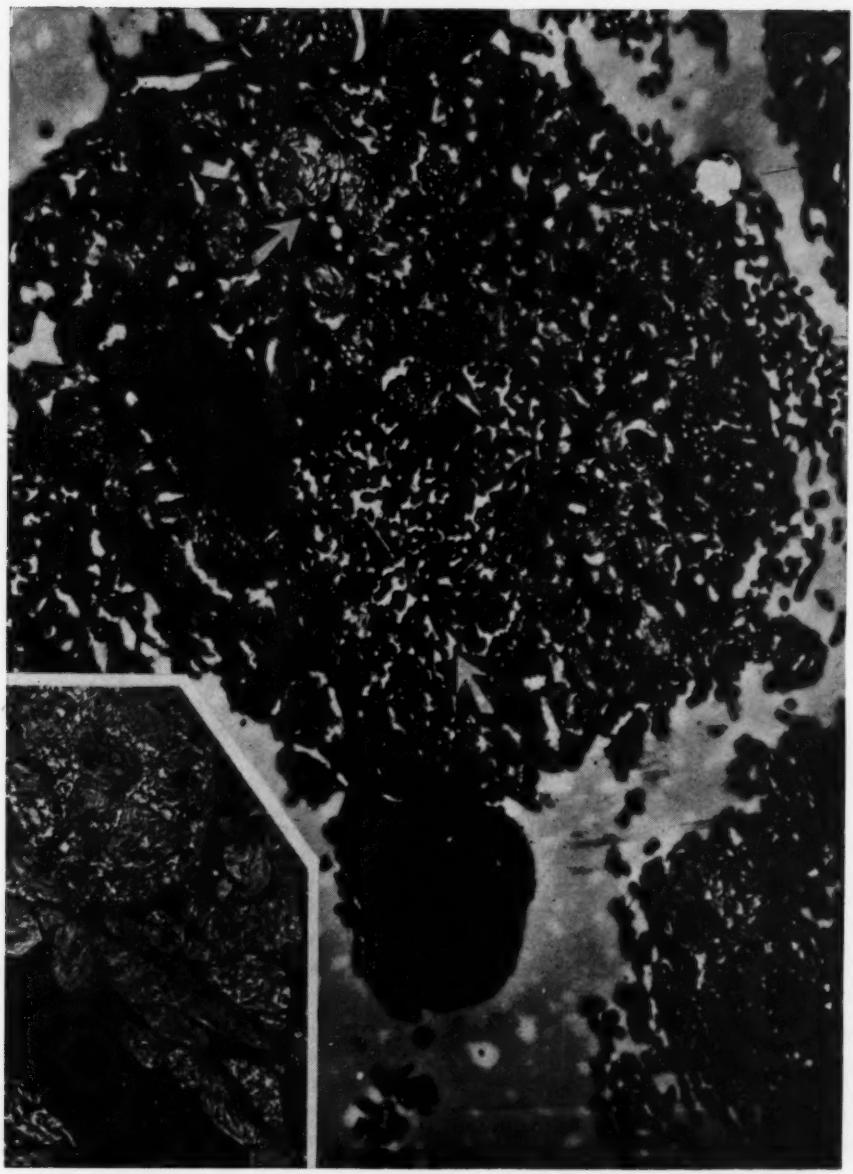

Figure 3

Electron micrographs of SPC cells illustrating the 2 forms in which the protein complex appears. The vacuolated clusters (*upper arrow* and *insert*) conform to the sickle-form particles. The aggregates of minute cylindrical bodies (seen in random sections at *lower arrow*) correspond to the amorphous cytoplasmic inclusions. Electron micrographs (about 7000x) by J. H. L. Watson, Ph.D., and Virginia Valentine of the department of physics, Edsel B. Ford Institute for Medical Research.

positive protein complex in the cytoplasm of plasma cells, Pearse[11] and later White[12] observed an inverse relation between the cytoplasmic content of ribonucleic acid (by pyroninophilia) and of the protein complex (by PAS-positivity). Teilum[13] demonstrated a similar relation in the cytoplasm of reticulo-endothelial cells proliferating in response to a variety of stimuli. According to Teilum, pyroninophilia and PAS-positivity represent characteristic phases in the functional activity of these cells by which protein complexes are formed. Applying the same cytochemical technics, Taft, Liddelow, and Ralston[14] in Australia reported a striking similarity in the staining reactions by the "frothy cells" of Whipple's disease to those observed in plasma cells by Pearse and by White and in reticulo-endothelial cells by Teilum. Taft *et al.* accepted this similarity as evidence that the PAS-positive substance of Whipple's disease is elaborated within the cytoplasm of the "frothy cells".

Accumulating evidence suggests, then, that the primary pathogenesis of Whipple's disease may be represented by the proliferation of peculiar SPC cells which are capable of elaborating within their cytoplasm an abnormal, PAS-positive, protein complex. The initial stimulus to this proliferation and elaboration remains unknown.

OTHER PROTEIN FORMING DISEASES

Pursuing further the concept of abnormal proteinaceous elaboration by cells derived from the reticulo-endothelial system, one can enumerate other diseases which may share this pathogenesis (Table I).

The commonest example of protein elaboration is that of antibody (globulin) formation by various cells of related origin, *i.e.*, by reticulo-endothelial cells, by plasma cells, and probably by lymphocytes, in response to infection or to antigen. In such instance, the elaboration is usually self-limited and, presumably, beneficial to the organism.

In other circumstances, the proliferation of abnormal cells and their elaboration of protein are often not controlled and represent a pathogenesis for disease. Macroglobulinemia furnishes an example in which abnormal protein substances are formed by cells proliferating, in some instances, autonomously (Mackay[15]). Myeloma is thought of as a neoplasm of plasma cells elaborating a type of globulin which may be deposited in visible quantities in the kidneys (Putnam,[16] Sanchez and Domz[17]). Myeloma, in turn, has been related to primary systemic amyloidosis on the basis of the proteinaceous material deposited in various tissues (Kyle and Bayrd[18]). Pulmonary alveolar proteinosis (Rosen *et al.*,[19] Harrison *et al.*[20]) is a relatively newly described condition in which a copious proteinaceous substance may be formed by the interalveolar "septal cells" which, it has been noted, occupy the same situation where SPC cells have been identified in Whipple's disease. Other conditions in which a similar pathogenesis may pertain include the reticuloendothelioses, certain hemolytic anemias (Osgood,[21] Sen Gupa *et al.*[22]), Hurler's disease (Jermain *et al.*[23]), and colonic histiocytosis in children (Rowlands and Landing[24]).

Obviously these various disease states are not characterized by a proliferation of precisely the same cells or by elaboration of the same protein complexes. The very fact that the cellular proliferations and their products are distinctive makes more

Protein Forming Diseases

TABLE I

Suggested examples of protein forming diseases.

Protein Substance	Probable Source	Disease
Antibody globulin	R-E cells plasma cells lymphocytes	various infections
Macroglobulin	lymphoid cells	macroglobulinemia
Myeloma protein	plasma cells	myeloma
Amyloid	plasma cells	primary amyloidosis
A mucopolysaccharide	septal cells	pulmonary alveolar proteinosis
A mucopolysaccharide	SPC cells	Whipple's disease

attractive the applicability of certain features of Burnet's clonal selection theory[25] as a possible mechanism leading to specific disease. In this concept, stated briefly, a potential variety of cells exists, ultimately derived from the reticulo-endothelial system, any one of which is capable, under an appropriate antigenic stimulus, of proliferating as a peculiar "clone" and of elaborating a specific, abnormal, protein substance. As such, a variety of diseases — of diverse etiologies, of diverse manifestations, and of diverse courses — might conceivably share a common pathogenesis.

SUMMARY

Whipple's disease is submitted as a prototype of an emerging concept of disease which is characterized by the proliferation of peculiar cells, seemingly derived from the reticulo-endothelial system, and elaborating within their cytoplasm abnormal protein substances.

REFERENCES

1. Haubrich, W. S., Watson, J. H. L., and Sieracki, J. C.: Unique morphologic features of Whipple's disease, Gastroenterology 39:454, 1960.

2. Whipple, G. H.: A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues, Bull. Johns Hopkins Hosp. 18:382, 1907.

3. Black-Schaffer, B., Hendrix, J. P., and Handler, P.: Lipodystrophy intestinalis (Whipple's disease), Am. J. Path. 24:677, 1948.

4. Puite, R. H., and Tesluk, H.: Whipple's disease, Am. J. Med. 19:383, 1955.

5. Sieracki, J. C.: Whipple's disease — observations on systemic involvment: I: Cytologic observations, AMA Arch. Path. 66:464, 1958.

6. Sieracki, J. C., and Fine, G.: Whipple's disease — observations on systemic involvement: II: Gross and histologic observations, AMA Arch. Path. 67,81, 1959.

7. Sieracki, J. C., Fine, G., Horn, R. C. Jr., and Bebin, J.: Central nervous system involvement in Whipple's disease, J. Neuropath. & Exp. Neurol. 19:70, 1960.

8. Eyler, W. R., and Doub, H. P.: Extra-intestinal roentgen manifestations of intestinal lipodystrophy, JAMA 160:534, 1956.

9. Mendeloff, A. I.: In discussion of (1) at 61st annual meeting of American Gastroenterological Association, New Orleans, April 1, 1960.

10. Cohen, A. S., Schimmel, E. M., Holt, P. R., and Isselbacher, K. J.: Ultrastructural abnormalities in Whipple's disease, Proc. Soc. Exp. Biol. & Med. 105:411, 1960.

11. Pearse, A. G. E.: The nature of Russell bodies and Kurloff bodies, J. Clin. Path. 2:81, 1949.

12. White, R. G.: Observations on formation and nature of Russell's bodies, Brit. J. Exp. Path. 35:365, 1954.

13. Teilum, G.: PAS positive reticuloendothelial cells producing glycoprotein, functional significance during formation of amyloid, Am. J. Path. 32:945, 1956.

14. Taft, L. I., Liddelow, A. G., and Ralston, M.:Whipple's disease: a clinicopathological study of 3 cases, Australasian Ann. Med. 8:129, 1959.

15. Mackay, I.: Macroglobulins and macriglobulinemia, Australasian Ann. Med. 8:158, 1959.

16. Putnam, F. W.: Plasma-cell myeloma and macroglobulinemia. I. Physiochemical, immunochemical and isotopic turnover studies of abnormal serum and urinary proteins, New Eng. J. Med. 261:902, 1959.

17. Sanchez, L. M., and Domz, C. A.: Renal patterns in myeloma, Ann. Int. Med. 52:44, 1960.

18. Kyle, R. A., and Bayrd, E. D.: "Primary" systemic amyloidosis and myeloma, Arch. Int. Med. 107:344, 1961.

19. Rosen, S. H., Castleman, B., and Liebow, A. A.: Pulmonary alveolar proteinosis, New Eng. J. Med. 258:1123, 1958.

20. Harrison, E. G., Jr., Divertie, M. B., and Olsen, A. M.: Pulmonary alveolar proteinosis: report of case with fatal outcome, JAMA 173:327, 1960.

21. Osgood, E. E.: Antiglobulin — positive hemolytic anemias, Arch. Int. Med. 107:313, 1961.

22. SenGupta, P. C., Chatterjea, J. B., Mukherjee, A. M., and Chatterji, A.: Observations on the foam cell in thalassemia, Blood 16:1039, 1960.

23. Jermain, L. F., Rohn, R. J., and Bond, W. H.: Studies on role of reticuloendothelial system in Hurler's disease, Clin. Res. 7:216, 1959.

24. Rowlands, D. T., and Landing, B. H.: Colonic histiocytosis in children, Am. J. Path. 36:201, 1960.

25. Burnet, F. M.: *The Clonal Selection Theory of Acquired Immunity*, Nashville, Tenn., Vanderbilt University Press, 1959.

THE USE OF PHENOTHIAZINES ON A GENERAL HOSPITAL PSYCHIATRIC SERVICE

ROBERT R. SCHOPBACH, M.D.*

It was thought valuable to review the manner in which phenothiazines are being used in the treatment of the various types of mental illnesses in an open psychiatric floor of a general hospital. The charts of all of the patients admitted to the psychiatric in-patient service of this 1000 bed private metropolitan hospital during the calendar year 1960 were reviewed to determine which phenothiazines had been given to each type of patient.

About half of the patients are admitted upon their own initiative or that of their relatives; half by referral from other physicians, and only a few by transfer from other hospitals. Commitment is only occasionally necessary during the early disturbed phase of an illness in order to retain the patient for necessary treatment. Note was made of all patients having been previously hospitalized in this or any other hospital. Similarly noted were subsequent readmissions to any hospital up until April 15, 1961. If a patient was admitted here again with 1960, only the data from the first admission was considered in this paper. A number of patients with chronic brain syndromes were transferred to nursing homes or other domiciliary facilities after their families had been reassured that everything possible had been done for them. Five senile patients died during their hospitalization. These individuals were admitted for an intercurrent illness but were housed on the psychiatric floor where the personnel were best trained to understand their needs. Likewise, if a month of intensive study and treatment produced no beneficial change in a chronic schizophrenic patient, the family was usually more able to accept transfer to a state hospital for long term care. For some it becomes financially impossible to maintain a relative in a private hospital after the 30 day Blue Cross limit expires but the number so forced to transfer is very small; nearly all are improved enough by then to be transferred to an out-patient status. Here the prevailing philosophy is to take the calculated risk of premature discharge and relapse by permitting patients to return to their homes (or the home of a congenial relative) as soon as it is reasonable and to be followed as an out-patient rather than demanding that they remain until it is certain that they are completely recovered and stabilized. If a patient understands that such an early discharge is a trial, he is not despondent nor resentful should an additional period of hospitalization prove necessary. Naturally, if the patient lives at a great distance, if the home situation is unsuitable, etc., such a plan would not be utilized. This philosophy accounts in part for the short hospital stays and for the high (18.5%) subsequent admission rate

*Division of Psychiatry.

even though those readmitted within two weeks were, for the purposes of this paper, considered as one admission.

The psychiatric service utilizes the entire ground floor of a wing which is divided into 24 single rooms, two recreation porches, and one large occupational therapy porch. Besides specially selected and trained nurses and auxiliary nursing personnel two graduate occupational therapists are daily urging patients to enter into activities which include not only handicrafts but various games, movies, and teas. There are six full time staff psychiatrists, two psychiatric residents, a medical resident, four psychologists, and a psychiatric social service worker in addition to the consultation facilities of a large general hospital with a permanent staff. This permits the most intensive of therapy.

The background of each of the psychiatrists is quite different yet there did not appear to be any major difference in the use of phenothiazines. Mellaril, Sparine, and Thorazine are used for their quieting effect upon the agitated portion of agitated depressions, alcoholic or drug withdrawal, or hypomania. The dose cannot be predetermined; enough must be given to do the job. Some physicians accustomed to their medical patients becoming somnolent on small amounts hesitate to prescribe the very large amounts necessary to calm an acutely disturbed person. Medical literature indicates that Thorazine tends to be more toxic than Sparine which in turn is more toxic than Mellaril. However, with such close supervision and the lowering of the dose as soon as possible, we have so few toxic reactions that no such choice could be justified. Of the 246 patients receiving these medications only one developed any side effect, marked hypotension with Thorazine. Nevertheless the possible occurrence of such reactions must always be kept in mind. These drugs also exert some suppression of disturbed mental processes but that is not their major value.

Compazine has a lesser sedative effect and a greater effect upon the mental processes. Stelazine, however, has even less sedative effect and a much greater effect upon disturbed thinking. As a result it is usually the drug of choice here for paranoid and delusional states, being prescribed in 64 of the 87 patients with paranoid ideation. In those schizophrenics who are withdrawn and retarded as a result of pan-anxiety Stelazine may alter their disturbed mental processes so that they may feel able to attempt increased activities and may perhaps become more amenable toward psychotherapeutic relations. With similar hopes Stelazine is administered to other types of schizophrenia. Some with relatively acute and florid symptomatology are markedly benefitted. Some of the chronic schizophrenic patients, who had been making a borderline adjustment prior to their present episode, were better able to disregard disturbing intruding thoughts and to regain their former level of adjustment. This was most clearly demonstrated in five paranoid schiziphrenic patients who suffered a

DIAGNOSIS	In-Patients January 1, 1960 through December 31, 1960						Received Phenothiazines											
													STELAZINE					
															Side Effects			Dose mg./day	
	MALE	FEMALE	TOTAL	PREVIOUSLY ADMITTED	SUBSEQUENTLY ADMITTED	AVERAGE STAY days	NONE	MELLARIL	SPARINE	THORAZINE	COMPAZINE	OTHERS	STELAZINE	STELAZINE PARANOID SYMPTOMS	PARKINSON	AKATHISIA	OTHER	RANGE	AVERAGE
SCHIZOPHRENIAS																			
Paranoid	10	33	43	13	12	17.0	0	4	4	7	2	0	33	33/43	2	2	0	3-20	12
Hebephrenic	0	1	1	0	0	8.0	0	0	0	1	0	0	0	0/0	0	0	0		
Catatonic	3	2	5	4	3	24.0	0	2	0	2	2	0	5	0/0	0	1	0	4-15	10
Undifferentiated	9	22	31	7	6	21.2	0	3	6	6	6	0	18	4/5	3	0	0	4-20	12
Other types	5	7	12	3	2	26.2	1	3	2	3	0	0	11	3/3	0	0	0	4-15	11
TOTAL	27	65	92	27	23	19.9	1	12	12	19	10	0	67	40/51	5	3	0		
Paranoid States	5	5	10	4	2	18.9	5	0	0	1	1	0	4	4/10	0	0	0	4-15	10
Manic-Depressive	4	8	12	11	6	12.0	2	1	0	5	1	0	2	0/0	0	0	0	10	10
DEPRESSIONS																			
Involutional	13	40	53	17	7	24.0	11	16	11	6	6	0	21	12/12	0	0	R	3-15	8
Psychotic	7	14	21	6	7	20.9	10	4	2	1	1	0	8	0/0	1	0	0	3-20	10
Neurotic	48	80	128	44	18	19.0	69	9	14	13	22	1	14	1/3	0	0	0	3-10	6
TOTAL	68	134	202	67	32	20.6	90	29	27	20	29	1	43	13/15	1	0	1		
NEUROSES																			
Obsessive-Compulsive	3	3	6	6	4	22.3	0	2	1	0	0	0	3	0/0	0	0	0	4-15	10
Anxiety reactions	19	57	76	28	15	14.9	28	8	16	10*	8	2	12	1/1	0	2	0	3-15	8
Psychophysiologic	1	7	8	1	1	15.7	5	1	1	2	0	0	0	0/0	0	0	0		
Other	9	19	28	8	1	15.0	10	8	6	1	5	0	5	1/1	0	0	0	2-15	9
TOTAL	32	86	118	43	21	15.4	43	19	24	13	13	2	20	2/2	0	2	0		
Personality Disorders	20	39	59	19	11	17.7	25	7	7	9	7	2	11	3/7	0	1	0	3-20	9
Alcoholism and D.T.'s	14	6	20	9	3	13.2	4	2	9	3	1	1	2	0/0	0	0	0	10-15	12
Acute brain syndrome	4	4	8	2	0	11.2	2	1	5	1	2	0	2	0/0	0	0	0	6-10	8
Chronic brain syndrome	12	17	29	4	3	19.9	10	6	6	6	3	0	3	0/0	0	0	0	8-15	11
Other diseases	3	3	6	3	2	10.5	2	1	1	2	0	0	2	2/2	0	0	0	10	10
GRAND TOTAL	189	367	556	187	103		184	77	91	78	67	6	156	64/87	6	6	1		

R = rash

* = 1 case of hypotension

recurrence of their delusions upon discontinuing (on their own) their Stelazine and who experienced a remission when the drug was recommenced. It does have some sedative effect which, in the higher doses, may be quite annoying. By prescribing it at bedtime the maximum sedation occurs at night and only helps provide a good night's sleep but the duration of action is such that the symptoms are kept in abeyance the next day with little if any sedation. This long duration of action is most fortunate for those patients who seem to have such difficulty remembering to take their medications a number of times per day. Five mg. Stelazine taken at bedtime is usually unnoticed by the patient. If they have been educated to the need for such suppressive medication, they will be willing to continue taking such an unobstrusive drug. If they have not accepted their need for drug help, they are likely to assume that since they are unaware of any drug effects that it is having no effect and will discontinue it.

Initially the dose is rapidly raised until the symptoms are controlled or until a side effect appears. With the relatively high doses of 15 - 20 mg./day 13 (8%) of the 156 patients receiving Stelazine developed such responses. The Parkinson-like rigidity, the muscle spasms, or the akathisia are very frightening to the patient but these all promptly disappear with anti-Parkinson drugs (Artane, Cogentin, or Kemadrin). It is usually advisable to temporarily discontinue or at least reduce the dose of Stelazine. To avoid such incidents when administering larger amounts one should prescribe concurrent doses of these anti-Parkinson drugs; in our experience, not a single person so treated developed any side effect. This drug is very potent and, if it is to be used for its maximum benefits, extremely close supervision is necessary. If the patient is not being seen daily, the higher doses must be approached much more gradually. After the acute phase has subsided, the drug may be slowly reduced. Just how long its administration should be continued is not certain. The author feels that after six months one may discontinue the drug while observing closely for any recurrence of symptoms.

A number of patients received more than one phenothiazine. An agitated and paranoid patient might initially receive one of the more "tranquilizing" drugs plus Stelazine but, when he had become calmer, the mild tranquilizing effect of the Stelazine might prove adequate and the other drug could be discontinued. Similarly, if the paranoid features disappeared but the patient remained tense, the milder antipsychotic action of this tranquilizing group might permit the Stelazine to be discontinued. Obviously this is a very individual matter requiring frequent re-evaluations during the acute phase of the illness and treatment.

The use of only five of the many phenothiazines does not imply that the others are necessarily inferior but rather that the staff has become familiar with these and sees no additional benefit in the use of the others.

With all phenothiazines the possibility of leucopenia and liver impairment must be considered and periodic white blood counts and transaminase tests performed. Discontinuance of the drug is usually all that is necessary should these appear. Should the symptoms recur it may be possible to administer a different phenothiazine although cross-sensitivity is frequent. If any other type of drug would be effective it should be given preference in such cases.

SUMMARY

The indications, dosages, side effects and results of various phenothiazines in a general hospital are statistically reported and described.

ACOUSTIC TRAUMA FROM A DOG TRAINING WHISTLE

HAROLD F. SCHUKNECHT, M.D.*
and
HENDRIK VAN DEN ENDE, E.E. (Delft)*

It is well-known that the inner ear may be injured from exposure to high intensity sound. This may result from a single shock pulse (such as a blast) or from prolonged exposure to high intensity sound (such as factory noise). It has recently been shown that a similar inner ear injury can result from a bone conducted shock pulse (sound wave) produced by a blow to the head.

The mechanism of injury is violent displacement of the basilar membrane resulting in disruption of the organ of Corti. The cells of the sense organ do not regenerate so that destruction of them results in permanent hearing loss.

Broad spectrum high intensity sounds usually produce the greatest injury in the basal turn of the cochlea in the area which serves the 4000 to 8000 cps frequencies. When the sound is sharply limited in its spectral characteristics, the inner ear usually is injured most severely in the area of the cochlea which responds to that frequency range.

The first symptom noted by patients exposed repeatedly to high intensity occupational noise is diminished hearing at the end of the work day with recovery after several hours. This condition is known as "auditory fatigue". Another symptom often distressing to the patient is "ringing" in the ears (tinnitus). These early symptoms should serve as a warning to individuals working in noise.

Further inner ear injury can be avoided by the use of protective ear plugs. Thus, when an individual experiences these early symptoms tests of hearing should be made and, when indicated, measurements should be made of the spectral characterictics and intensity of the sound environment so that appropriate protective measures can be instituted.

An unusual case which came to our attention recently was that of a trainer of hunting dogs who noticed a progressive hearing loss. He constantly used a whistle which was audible to the human ear. We analyzed the spectral and intensity dimensions of the whistle noise to establish more clearly the relationship of the hearing loss to his occupation.

The patient had been training hunting dogs for about five years and noticed for several months that at the end of a long day of work his hearing was diminshed and that recovery occurred after several hours rest. He preferred to use the louder of two whistles in his possession because the dogs were more responsive to it. He was aware of the probable relationship between the whistle and the hearing loss, and had worn protective ear plugs intermittently. He did not persist in their use, however, because while wearing them he felt somewhat handicapped in the execution of his work. He also used a gun during some of the training sessions, discharging it repeatedly during these periods. Characteristically, hearing losses resulting from shotgun fire

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result in a greater loss in one ear than the other, this being due to the position of the head in relation to the muzzle blast. Thus, for an individual shooting from the right shoulder, the loss is always greater in the left ear.

For our patient, the audiometric thresholds for the two ears were symmetrical. Therefore, we believe that his hearing loss is due to the whistle which exposes both ears symmetrically and not to the shotgun blasts which would expose the ears asymmetrically.

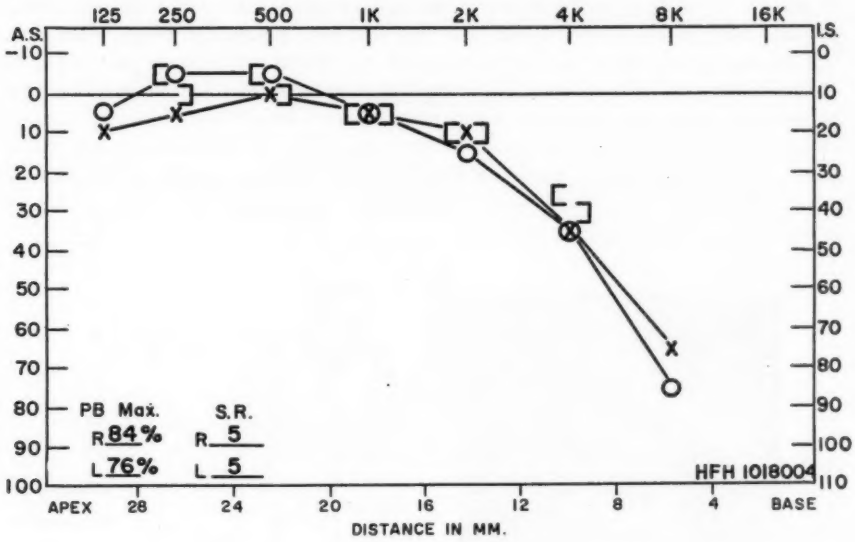

Figure 1
Audiogram showing hightone sensorineural hearing loss.

Examination revealed normal ear drums. He heard the 512 cps tuning fork better by air conduction than by bone conduction on both sides. Audiometry revealed a bilateral symmetrical high tone sensorineural type deafness with speech discrimination scores (PB-Max) of about 80 percent and speech reception thresholds of 5 db. (See Fig. 1)

The whistle shown in Fig. 2 has a cork ball in its cylindrical cavity. This cork ball whirls around when the whistle is blown.

On a sunny day, with little wind, the equipment of Fig. 3 was arranged on the roof parking area of the Henry Ford Hospital garage so as to determine the sound pressure levels produced by the high pitched whistle outdoors, at the entrance of the external meatus. After adjusting the equipment, the operator would then walk over to the microphone stand, a distance of approximately 10 yards, and would position himself so that the microphone was approximately 2 in. in front of the external meatus of his right ear, and blow the whistle.

The analyzer was first adjusted to have a pass band 20 - 35,000 cps to determine the overall sound pressure level. The whistle was blown three times, each blast lasting two seconds. Fig. 4 (upper trace) shows the recording thus obtained. The three blasts "rise" out of a 71 db background noise, which was attributed to highway traffic and perhaps some wind. The overall blast sound pressure level was 101 db in one series and 108 db in another series of tests.

The analyzer was then adjusted so as to pass a narrow band of frequencies only. The center frequency (fc) of this band was then automatically scanned from 200 - 20,000 cps by coupling to the motor of the level recorder which simultaneously moves the recording paper. The analyzer is of the constant percentage band width type, and the octave selectivity was adjusted for 40 db, hence the response was down by 40 db at 2 fc and ½ fc independent of the value of fc; series of blasts were recorded on two occasions, the maximum sound pressure level was 101 db on one occasion (Fig. 4, middle trace) and 108 db on the other (Fig. 4, lower trace). A steady 4000 cps tone of proper intensity with 10 percent second and 3 percent third harmonic content instead of the whistle would produce the envelope of the blasts of Fig. 4, middle trace.

Figure 2
Dog training whistle.

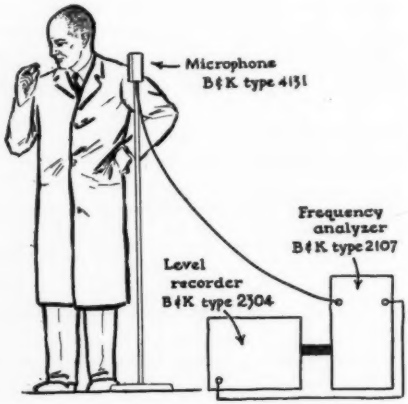

Figure 3
Arrangement of sound recording equipment.

The sound pressure level spectrum of the whistle consist therefore of a sharp 4000 cps peak of 100 - 108 db with second and third harmonic peaks of approximately 80 and 70 db respectively, and those peaks are probably much narrower than suggested by Fig. 4. Following the tests, the operator (H. v. d. E.) experienced a slight subjective sensation of auditory "stuffiness" for several hours and high pitched tinnitus for about 12 hours.

High frequencies are known to be more damaging to the inner ear than low frequencies and for the 4000 cps range the maximum intensity considered to be safe in the military and industry is about 85 db.

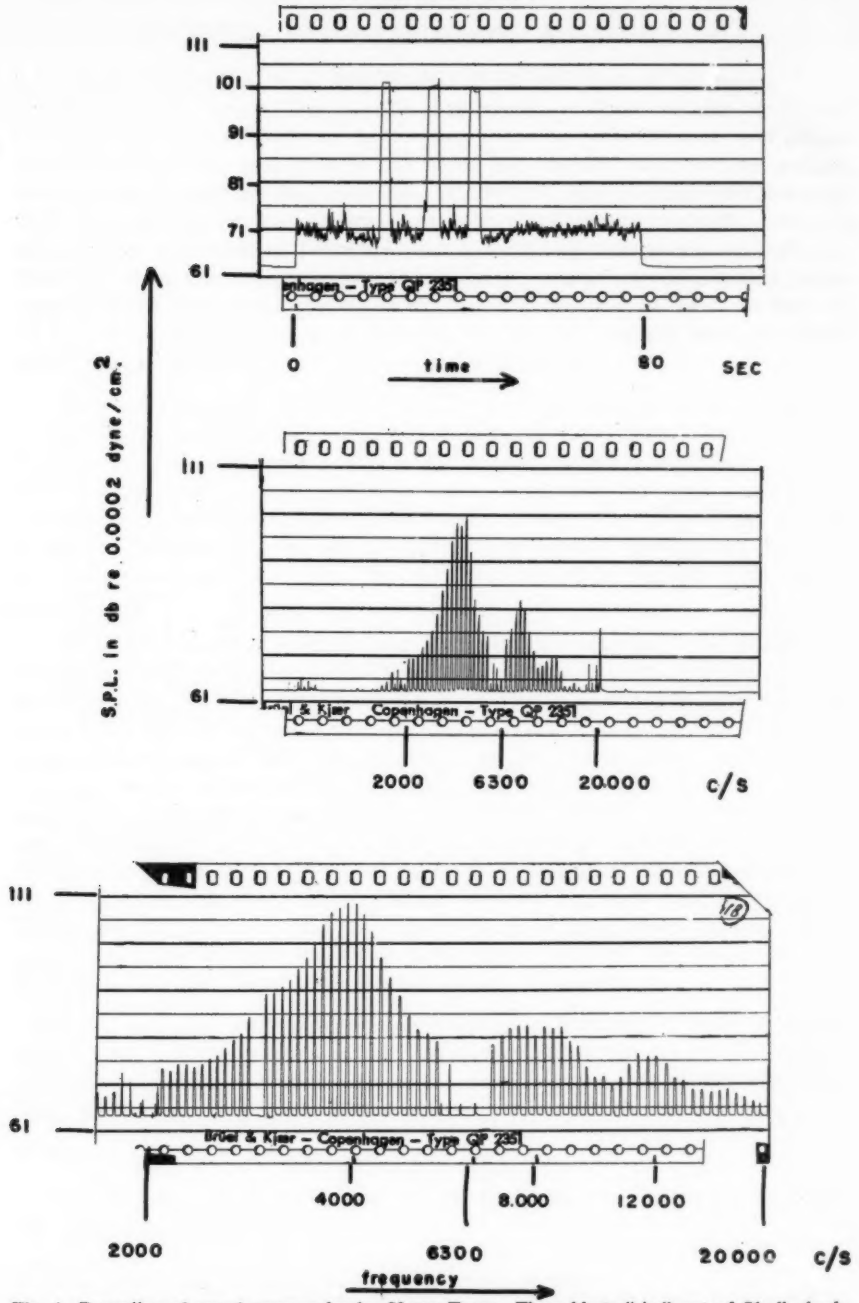

Fig. 4. Recording of sound pressure levels. Upper Trace: Three blasts "rise" out of 71 db, background noise. Passband 20 — 35.000 cps. Paperspeed 1mm/sec. Middle Trace: A series of blasts recorded while scanning the frequency range with a narrow passband. Paperspeed 0.3 mm/sec. Lower Trace: As middle trace but paper speed 1.0 mm/sec.

SUMMARY

A trainer of hunting dogs used a shrill whistle as a command signal. He experienced tinnitus, auditory fatigue and, after several years, a mild, permanent hearing loss. An analysis of the sound spectrum of the whistle revealed overall sound pressure levels of about 101 and 108 db on two separate tests. Narrow band analysis showed a sharp pressure peak at 4000 cps and lesser peaks for the second and third harmonics. Commercially available protective ear plugs of proper size have been prescribed for the patient, and he has been instructed to wear them at all times during exposure to the whistle noise. Fortunately, protective ear plugs are more effective for high frequencies than for low frequencies, and they should prevent further inner ear injury.

THE ADVANTAGES OF VESTOPAL W. AS AN EMBEDDING MATERIAL FOR BIOLOGICAL AND MEDICAL ELECTRON MICROSCOPY

ROBERT R. CARDELL, JR.*

INTRODUCTION

The rapid growth of biological and medical applications of electron microscopy has been possible through significant advancements in sectioning techniques. Sections less than 500 A thick are required for study with the electron microscope, and thus some means of producing such ultrathin sections was the primary requirement in the application of this instrument to biological material. Porter and Blum[1] were among the pioneers in the development of an ultramicrotome, and currently there are several types of ultramicrotomes available for ultrathin sectioning.[2]

The second necessity for ultrathin sectioning is a sufficiently sharp cutting edge to slice the material. Sjostrand[3] developed a technique for further sharpening razor blades to the desired sharpness; Latta and Hartman[4] discovered that glass could be broken in a particular way to produce a cutting edge sharp and perfect enough for cutting ultrathin sections; Fernanez-Moran[5] experimented with and perfected the use of polished diamond chips as cutting surfaces. The electron microscopist, therefore, now has a number of cutting edges that will produce ultrathin sections of the desired thickness.

In order to produce ultrathin sections of biological material, it is necessary to embed the tissue in a medium harder than the paraffin used in tissue preparation for light microscopy. The use of the polymer, methacrylate, as described by Newman *et al*,[6] was a major step in the development of biological and medical electron microscopy. Methacrylate is used in most electron microscopy laboratories today, but this is far from the perfect embedding medium. Since fine cellular structure is not ideally preserved by this plastic, the search for a substitute for methacrylate continues. Maale and Birch-Andersen[7] have used epoxy resins and Kellenburger *et al*[8] have experimented with certain polyesters. Lack of contrast in epoxy-embedded tissue necessitates the use of additional "electron stains" in order to obtain high resolution electronphotomicrographs. The polyesters offer more contrast than the epoxy resins but less contrast than methacrylate. In 1958 Ryter and Kellenburger[9] described the use of polyester Vestopal W. for their work with ultrathin sections of bacteria.

In our laboratory we have been experimenting with Vestopal W. as an embedding medium and it is the purpose of this report to compare the results of Vestopal-embedded material to methacrylate-embedded material. Human skin* and salamander pituitaries are used to illustrate the advantages of Vestopal over methacrylate.

MATERIALS & METHODS

The procedure for both the skin and the pituitaries was similar therefore they will be described together.

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*The skin specimen was obtained by Dr. Hu, Department of Dermatology, and a more detailed report on the ultrastructure of the skin will be reported in a later publication.

For methacrylate embedding, the tissue was fixed for two hours in buffered 1% osmium tetraoxide (pH.7.4), dehydrated in a graded series of alcohol, and infiltrated with 3:1 butyl to methyl methacrylate. The specimen was placed in gelatin capsules containing catalized methacrylate (2% Luperco CDB) and allowed to polymerize in an oven at 65°C for twenty-four hours. After the methacrylate had hardened the gelatin capsule was removed and the specimen trimmed in the shape of a truncated pyramid. Ultra-thin sections were cut on a Porter-Blum ultramicrotome or on a LKB ultratome using either glass knives[4] or a polished diamond chip.[5] The sections were placed on #100 Athene grids which were previously coated with a thin film of parlodian and carbon. The sections were viewed with a modified RCA electron microscope and electronphotomicrographs were taken of selected area.

The procedure for the Vestopal W.-embedding is similar to the methacrylate-embedding procedure except that acetone is used for the dehydrating agent, since vestopal is not miscible with alcohol. (It is necessary to dry the acetone over copper sulfate to insure that all the water is removed from the acetone, for if water remains

LIST OF ABBREVIATIONS

pcn	Parenchyma Cell Nucleus
ps	Perisinusoidal Space
sg	Secretory Granule
gg	Gonadotrophic Granule
m	Mitochondria
ga	Golgi Apparatus
psc	Perisinusoidal Cell Cytoplasm
f	Fibroblast
cf	Collagen Fibers
mg	Melanin Granules
bcn	Basal Cell Nucleus
bm	Basement Membrane

FIGURE 1

Salamander pituitary gland embedded in methacrylate. This is a section through the perisinusoidal space showing two parenchyma cells bordering this space. Note the large intercellular spaces (between arrows) and the discontinuous cell membranes. The secretary granules (sg) and the gonadotrophic globules (gg) of the parenchyma cells are shown. The reader should compare this electron micrograph with figure 2 and 3. (12,000X)

FIGURE 1

in the tissue, bubbles are formed during the embedding procedure.) Vestopal W. is much more viscous than methacrylate and requires a longer time for the infiltration process. The author infiltrates the tissue over a twenty to twenty-four hour period. The tissue is then placed in gelatin capsules and placed in an oven for twenty-four hours. The preparation of the ultrathin sections is similar to that described above for methacrylate-embedded specimens.

RESULTS & DISCUSSIONS

In a study of the ultrastructure of the pituitary gland of the salamander *(Triturus viridescens)*[10,11] the author was interested in the ultrastructure of the cell types of the *pars distalis,* and in the relationship of each cell to each other and to the circulatory system of the pituitary. Obviously it is imperative in a study of this nature that the embedded material under study be consistent from one preparation to another. With methacrylate-embedded specimens one could not be confident that such consistency always was obtained.

FIGURE 2

Salamander pituitary gland embedded in Vestopal W. This is a section through the perisinusoidal cytoplasm with several different parenchyma cells bordering the perisinusoidal cytoplasm (psc). Compare the continuous cell membranes of this preparation to the broken cell membranes of the parenchyma cells in figure 1. Also note the well preserved mitochondria (m) and the lack of large intercellular spaces. (12,000X)

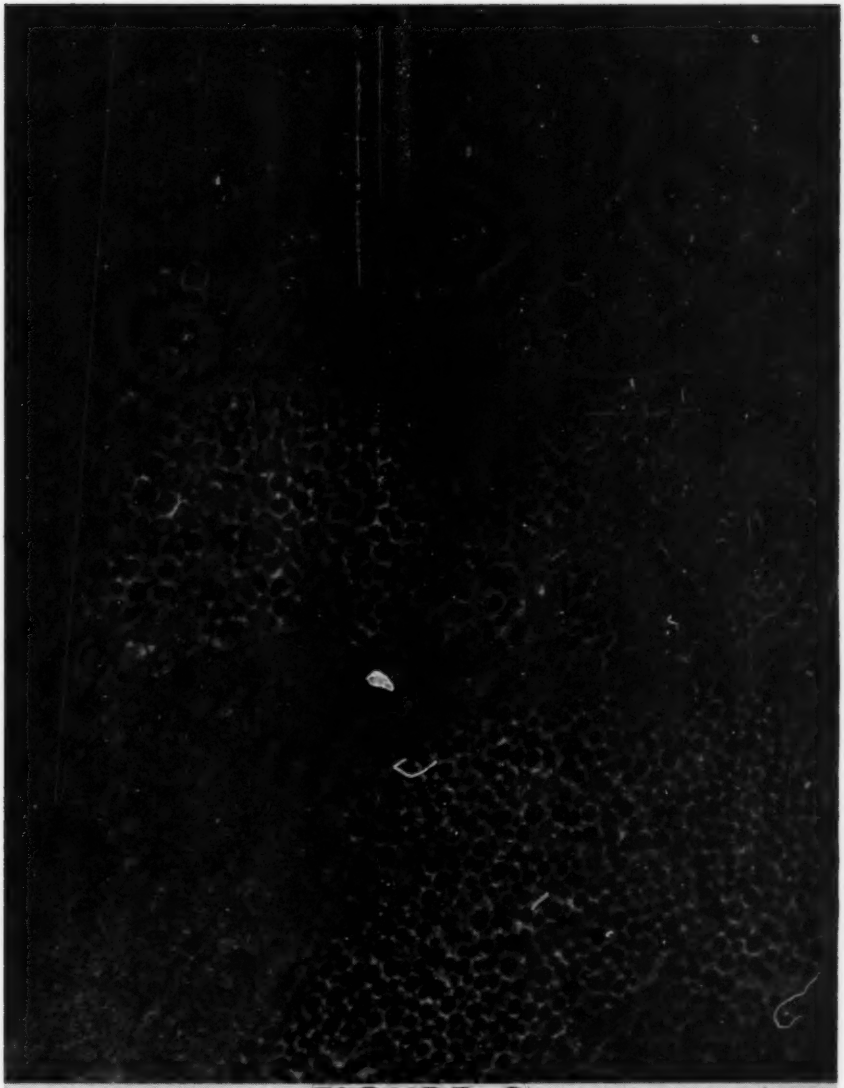

FIGURE 2

To illustrate, figure 1 is an electron micrograph of a section through the perisinusoidal space with three parenchyma cells bordering it. This material was embedded in methacrylate and as one studies this preparation it is obvious that considerable amount of cell shrinkage has occurred. Notice the space between the cells and the broken cell membrane. The fine structure within the cell gives the appearance of "poorly fixed" material. The author attempted to improve the quality of the preservation of the material by altering the fixation procedure in various ways, but significantly improved results were not obtained consistently. Therefore, attention was given to the embedding material. It was soon apparent that by changing no procedure in the preparation other than substituting acetone for alcohol and Vestopal W. for methacrylate, the preservation of the fine structure of the cells could be improved greatly, and cell shrinkage eliminated. Consistently good preparations were thus obtained enabling the study of the ultrastructure of the cells and the cell relationships, without the artifacts characteristic of methacrylate-embeddings. To illustrate this difference, note figure 2 which is a section through the perisinusoidal cell with four parenchyma cells bordering the cytoplasm. The reader's attention is directed to the complete lack of cell shrinkage as evident by the cell membrane being separated from

FIGURE 3

A higher magnification of parenchyma cells bordering perisinusoidal cytoplasm (psc). Note the improved (compare with figure 1) preservation of the cytoplasmic structures as shown by the endoplasmic reticulum, cristae of the mitochondria (m) and the Golgi apparatus (ga). The small intercellular space is shown between the arrows. (31,000X)

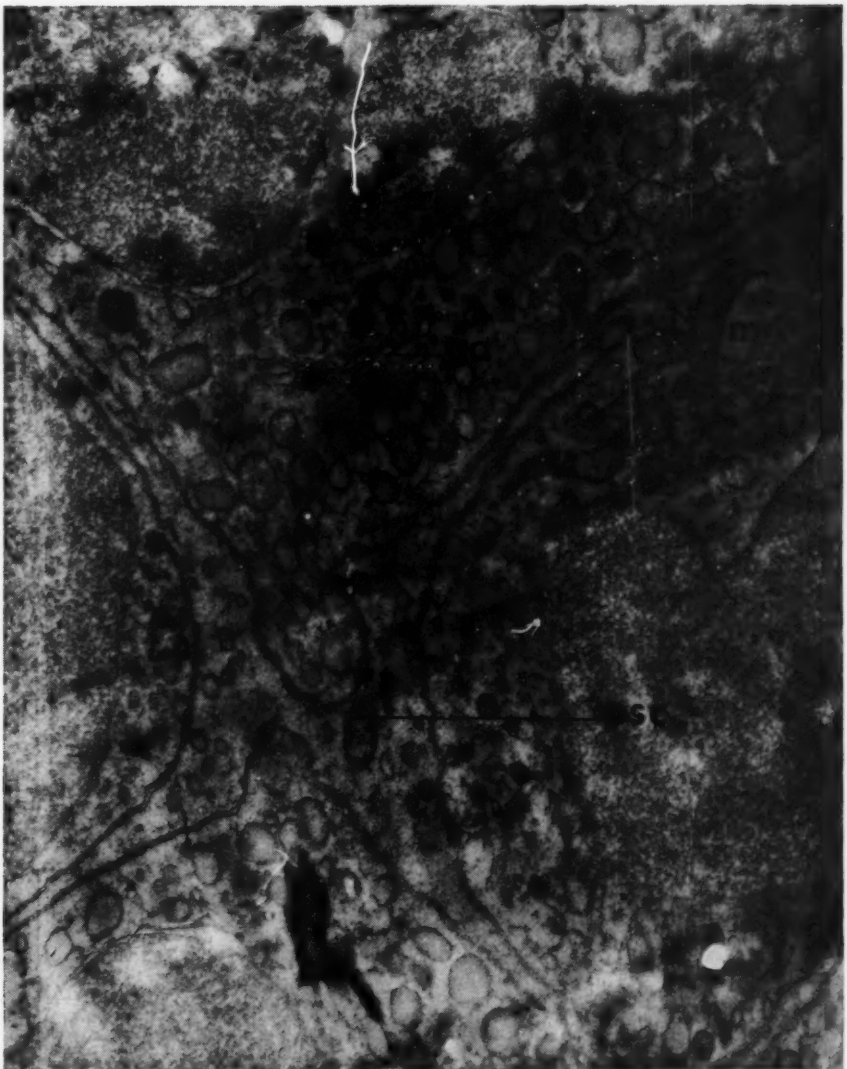

FIGURE 3

each other by a small distance (.03μ); and also note the continuity of the cell membrane. Within the cell the mitochondria are well preserved showing the characteristic organization of mitochondria, and the Golgi apparatus is well defined.

Human skin presents particular problems to the electromicroscopist in that the ultrastructure is difficult to preserve and good sections are not easily obtained. In a study of normal human skin it was found that Vestopal W.-embedded specimens showed the cellular fine structure much better preserved; clearly defined, continuous cell membranes; unbroken, conspicuous membranes (Fig. 3); and well-resolved collagen fibers of the dermis (Fig. 4). This is in sharp contrast to the methacrylate-embedded specimens in which it is very difficult to study these structures. It should be pointed out in the study of the skin that it is necessary to add phosphotungstic acid as an additional "electron stain" to improve the contrast of the specimen.

Vestopal W. is not restricted to the examples illustrated above but has been used by the author for thyroid, lung, human pituitary tumor, dog pituitary and crayfish testis tissue with essentially similar results as described above.

FIGURE 4

Human skin embedded in Vestopal W. The basement membrane is clearly shown (follow the series of arrows) and it is unbroken. The basal cell of the epidermis contains melamin granules (mg) and the cells do not appear to be shrunken. Note the well preserved collagen fibers (cf) and the fibroblasts (f) of the dermis. (12,000X)

FIGURE 4

Finally, a technical advantage of using Vestopal W. is that the sections may be cut thicker than with methacrylate without sacrificing good resolution. Other than the advantage of having to strive for extremely thin sections, there is also the advantage of being able to produce sections with a greater area in each section. For example, with methacrylate it is extremely difficult to cut sections much greater than 0.5^2 mm. but with Vestopal it is possible to cut sections 1.0^2 mm. and still produce pictures with high resolution. This increases the area of tissue available for study four times per section and is of considerable value when one wishes to study several different areas in a given tissue.

It should be pointed out, however, that vestopal W. is more difficult to section. While this is annoying during the sectioning process, it is the author's opinion that the improved results are well worth the extra work during the sectioning procedure.

FIGURE 5

A section through the dermis of human skin embedded in Vestopal W. Note the regular packing of the collagen fibers. (12,000X)

FIGURE 5

SUMMARY

Vestopal W. has been compared to methacrylate as an embedding material for electron microscopy. Evidence is presented which shows that Vestopal W.-embedded specimens have less cell shrinkage, better preservation of fine structure within the cells, the membrane structure and cytoplasmic inclusions are better preserved and in general the results with Vestopal W. are more consistent from preparation to preparation than those with methacrylate. It is noted that sections of methacrylate-embedded specimens possess much more inherent contrast than Vestopal embedded material.

REFERENCES

1. Porter, K. R., and Blum, J.: Study in microtomy for electron microscopy, Anat. Rec. 117:685, 1953.

2. Gettner, M. E., and Ornstein, L.: Microtomy, In, Oster, G., and Pollister, A. W. eds.: Physical Techniques in Biological Research, New York, Academic Press, 1956, v. 3 pp. 627-686.

3. Sjostrand, F. S.: A new microtome for ultrathin sectioning for high resolution electron microscopy, Experientia 9:114, 1953.

4. Latta, H., and Hartmann, J. F.: Use of a glass edge in thin sectioning for electron microscopy, Proc. Soc. Exper. Biol. & Med. 74:436, 1950.

5. Fernández-Morán, H.: Applications of a diamond knife for ultrathin sectioning to the study of the fine structure of biological tissues and metals, J. Biophys. & Biochem. Cytol. 2:29 (Suppl.) 1956.

6. Newman, S. B., Borysko, E., and Swerdlow, M.: Uutra-microtomy by a new method, J. Research Nat'l. Bur. Stand. 43:183, 1949.

7. Maale, O., and Birch-Andersen, A.: On the organization of the 'nuclear material' in *Salmonella* typhimurium, Symposium Soc. Gen. Microbiol. 6:261, 1956.

8. Kellenberger, E., Schwab, W., and Ryter, A.: L'utilisation d'un copolymére du groupe des polyesters comme material d'inclusion en ultramicrotomie, Experientia 12:421, 1956.

9. Ryter, A., and Kellenberger, E.: L'inclusion au polyester pour l'ultramicrotomie, J. Ultrastruct. Research 2:200, 1958.

10. Cardell, R. R., Jr.: Observations on the structure and ultrastructure of the pituitary gland of the salamander (*triturus viridescens*), ASB Bulletin 8:27, 1961.

11. Cardell, R. R., Jr.: Observations on the ultrastructure of the *Pars distalis* of the pituitary gland of the salamander (triturus viridescens), J. Applied Physics (To be published).

VISUAL HALLUCINATIONS IN CEREBRAL LESIONS: A CASE REPORT

V. N. SAMUEL, M.B.B.S., M.S.*

Hitzig[1] in 1874, and Ferrier[2] in 1875, experimentally outlined the visual cortex and showed that the projection fibers of the optic pathways were confined to the occipital lobe. Jackson and Beevor in 1899[3] reported visual hallucinations in one of their cases in which autopsy disclosed a tumor of the tip of the temporal lobe. Jackson and Beevor, therefore, were the first to show that visual hallucinations could arise from lesions of the temporal lobe. However, Henschen[4] in 1890 published reports of 16 cases of visual hallucinations and correlated these to irritative lesions of the cortex of the occipital lobe. Kennedy[5] in 1911 postulated that visual hallucinations might occur from reawakening of infantile memories stored in the temporal lobe by irritation produced by tumorous involvement of that lobe. In 1921, Cushing[6] found visual hallucinations in 13 cases from a group of cases of tumor of the temporal lobe. He postulated that hallucinations were produced by irritation and destruction of the geniculocalcarine bundle in the temporal lobe. Kennedy,[7] in discussing Cushing's paper, remarked that in his opinion crude spectroscopic hallucinations were found only in association with lesions of the occipital lobe, and the complex type only in association with lesions of the temporal lobe. This view was strengthened by the findings of Horrax and Putnam,[8] who studied a series of cases of tumor of the occipital lobe and concluded that crude visual hallucinations were seen in such lesions. Bender and Kanzer[9] in 1941 suggested the parieto-occipital region as being the site of origin of visual hallucinations in association with other psycho-visual disturbances, such as visual inattention, spatial disorientation, micropsia, macropsia, object agnosia and polyopia. They cited Foerster's[10] observations: that stimulation of area 17 of Brodman produced simple visual hallucinations; that when area 19 was stimulated, the hallucinations were more complicated and that, if area 17 was stimulated for a prolonged period, initial unformed hallucinations changed into more complex forms.

Penfield[11] reported that stimulation of the occipital cortex close to the posterior end of the calcarine fissure, when compared with stimulation of the outer convexity of the rest of the occipital lobe, surprisingly produced few differences. The descriptions used by patients following stimulation were flickering lights, dancing lights, bright lights, wheels, blue-green, and red colored discs, and so forth. He concluded that electrical or epileptic stimulation in the primary (area 17 of Brodman) and the secondary fields (areas 18 and 19 of Brodman) produces visual phenomena which are identical in character. However, he points out that the secondary visual cortex is probably a field for visual elaboration, and also that in general the calcarine image was more often colored while images produced from the secondary visual zone more often consisted of colorless light. He was able to reproduce in man complex physical illusions and hallucinations by electrical stimulation of certain areas of the temporal lobe.

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Even though it is generally accepted that visual hallucinations are essentially central phenomena produced by cortical irritation, there are some authors who have reported these in lesions of the optic tract, chiasm, optic nerve and retina. Among them, mention may be made of Jolly,[12] Pick,[13] Posey and Spiller,[14] Fay[15] and Terson[16] between 1902 and 1930. In 1940, Weinberger and Grant[17] reviewed the literature on visual hallucinations and studied these phenomena in 129 cases of verified adenoma of the pituitary and 84 cases of hypophysial duct tumor. Among this group there were 16 cases of visual hallucinations. They concluded that visual hallucinations have no localizing value, but only represent psychological phenomena involving the total integrative activity of mind. They also indicated that the complexity of the images depends upon constitutional factors and not on cortical psychic organization.

Walsh[18] does not agree in toto with the concept of Weinberger and Grant. He refers to the works of several authors who have reported visual hallucinations in ocular disorders such as removal of an eye, retinal hemorrhage, glaucoma, optic atrophy due to tabes, cataract before and after extraction, detachment of the retina, toxic states and also psychopathies. However, he concludes that "there are too many cases which support the proposition that formed hallucinations may arise as the result of temporal lobe involvement and that unformed ones may originate in involvements of the occipital lobe, to accept new evidence without its being further substantiated".

Schneider and Crosby[19] have observed visual hallucinations occurring in lesions involving or compressing the connection between the temporal and frontal lobe and in particular the uncinate fasciculus.

The following case illustrates the above possibility:

Mrs. D. S. is a 29 year old lady who was first seen in the Neurology Clinic on August 5, 1959. Her chief complaint was poor vision for two to two-and-one-half years. She had developed a blind spot in her left eye a year ago, centrally, which enlarged later and included most of the visual field except for the extreme nasal portion of the left eye. She said that vision in her right eye was not very good. Besides defective vision she also complained of formed visual hallucinations for over 9 months. She reported that she saw repeatedly eyes, snakes, spiders and birds. She saw the shadow of a man who had no face or arms, wearing a hat and an overcoat with two huge green eyes carrying snakes on his arms and dropping them on her. She saw huge spiders as big as a house and snakes as long as two miles in the sky. She often saw snakes scattered over the floor and walls and pre-historic birds zooming across the sky at her. Images were identical and not restricted to any particular portion of the visual field. She denied diplopia or halo vision. She also denied auditory, olfactory or gustatory hallucinations and also did not complain of any thought disturbance or convulsions. She did report a vague sub-occipital headache. Past medical history revealed that her left ovary, the site of a benign tumor, was removed in 1953. Menses had become scanty and irregular during the past 3 years and marked obesity had been present for over 13 years. She admitted to taking alcohol in varying amounts from time to time.

General physical examination was not remarkable except for significant obesity. Height 5'5½", weight 229 pounds, B.P. 180/110. Pulse 96/min. and regular. Positive

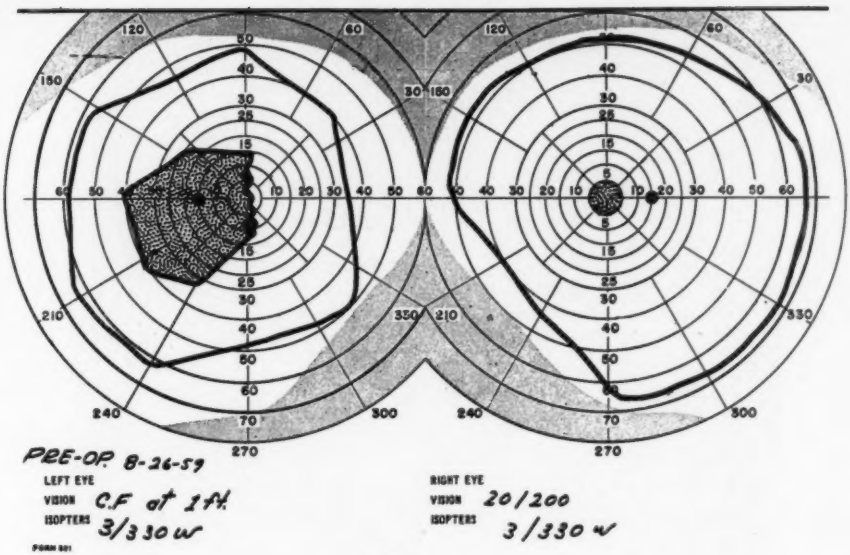

Figure 1

Preoperative visual field showing on the left irregular concentric constriction and a large scotoma.

neurological findings were confined to her visual system. Visual acuity O.S. was reduced to counting fingers at one foot and O.D. 20/200. Visual fields O.S., the patient was able to see a moving finger nasally, but unable to see a second finger simultaneously brought in from the temporal field except when it was brought in far superiorly and temporally, and O.D. appeared to be full peripherally. Ophthalmoscopic examination revealed a normal fundus on the right and temporal pallor on the left. Macular and other areas on both sides appeared to be within normal limits. Pupils were equal, round, regular, reacting to light and accommodation. There was no ptosis, diplopia or nystagmus. Extra-ocular movements were full. X-ray of skull and EEG were negative and spinal fluid findings, including pressure, were within normal limits.

She was referred to the Ophthalmology Clinic where visual fields were done peripherally using a 3/330 white object (Fig. 1). On the right, the peripheral field seemed reasonably full though there was a scotomatous area in central 5° circle. On the left, there was irregular concentric constriction with a large scotoma extending from the fixation area temporally past the blind spot. Attempts to obtain central fields on a tangent screen were unsuccessful. With a Guyton perimeter, on the right, there was just a suggestion of loss of the lower nasal quadrant when extinction technique was employed. A tumor in the region of the pituitary stalk was suspected.

She was admitted to the hospital on September 28, 1959, at which time she had pneumoencephalogram and bilateral carotid arteriograms. Pneumoencephalogram (Fig. 2) revealed a suprasellar mass deforming the anterior portion of the third ventricle.

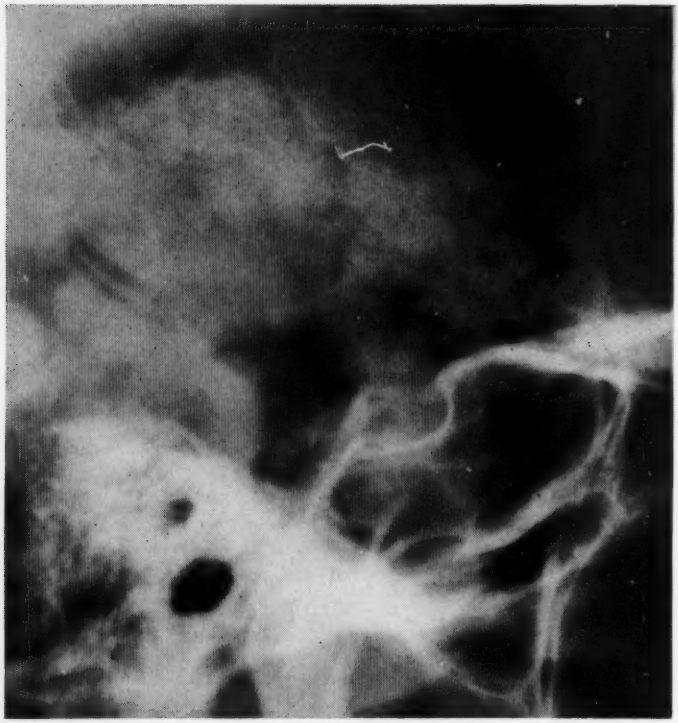

Figure 2

Pneumoencephalogram, lateral view, showing deformity of the anterior portion of the third ventricle.

Right carotid arteriogram (Fig. 3) showed the right anterior cerebral artery curving upwards gently on leaving the carotid and approaching the midline. The endocrine evaluation was limited to observations on the levels of free 17-hydroxycorticoids in plasma. The normal diurnal change in concentration was noted.

A left frontal craniotomy was done and the tip of the left frontal lobe was amputated for better exposure of the field. The supra-chiasmatic cistern was opened and on exploration of this region, a tumor 3 cms. in diameter was found over the left optic nerve, extending from the posterior olfactory groove to the clinoid process and part of it into the sella. The left optic nerve was decompressed by removing part of the tumor; however, no attempt was made to do a total excision and it was decided to do further removal as a second stage. The right optic nerve was not exposed. The tumor was reported as meningioma. She had an uncomplicated postoperative course except for the onset of diabetes insipidus, which was treated appropriately. Re-evaluation by Ophthalmology on the 9th postoperative day revealed marked visual improvement (Fig. 4). Her visual acuity had improved to O.D. 20/30 and O.S. 20/200. Visual fields, O.D., within normal limits. There was no suggestion of a nasal field loss even with 2 target test technique. O.S. showed an absolute scotoma of the

Figure 3

Right carotid arteriogram showing the right anterior cerebral artery curving upwards gently on leaving the carotid and approaching the midline.

central field to 5°, and a relative inferior temporal field defect which extended from the central field to about 40° horizontally and to the midline vertically. With a red object 3/330, the patient had only a small field remaining in the inferonasal quadrant extending from approximately 10° to 20°. Her last visual field recording was done on May 17, 1960, and this showed only a small scotoma which was essentially relative, located just below and temporal to the fixation point in the left field, the right field being full. She continues to do well and has never had hallucinations from the time of her surgery. Her menstrual periods, which spontaneously returned in January, 1960, have continued at intervals of 35 to 38 days. When last seen on June 12, 1961, she said that she was still free of visual hallucinations.

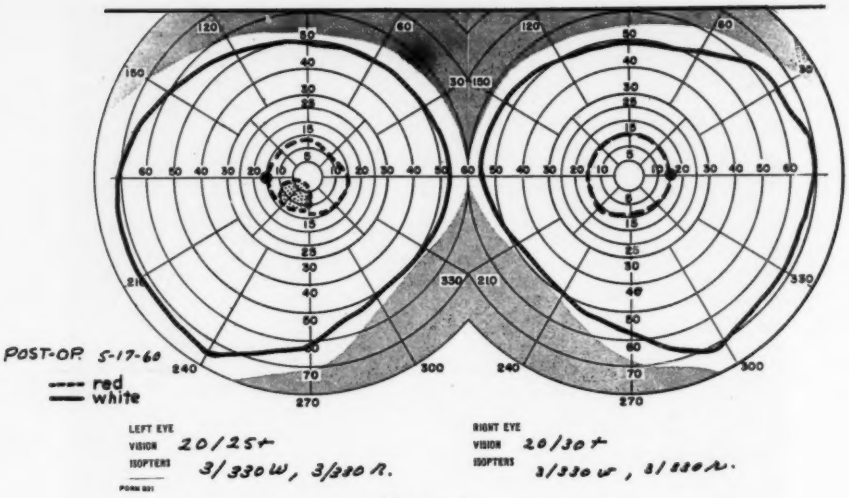

Figure 4

Postoperative visual field showing marked improvement.

SUMMARY

A case is presented of formed visual hallucinations in a 29 year old woman relieved by removal of a meningioma in the chiasmatic region and attached to the left optic nerve. Her symptoms are considered to be of temporal lobe origin and probably due to pressure on the uncinate fasciculus. The role of frontal lobectomy in this case is not clear, but it does not appear that at any time the frontal lobe itself originated the discharge. However, removal of the orbital area would destroy the cells of origin for many frontotemporal components of the uncinate fasciculus. Such fibers would degenerate and, even if there were a possible source of irritation remaining along the course of the fasciculus, it could no longer discharge to the temporal lobe over degenerated fibers.

REFERENCES

1. Hitzig, E.: Untersuchungen Über das Gehirn, Berlin, A. Hirschwald, 1874.

2. Ferrier, D.: Experiments on the brain of monkeys, Phil. Tr., London 165:433, 1875.

3. Jackson, J. H., and Beevor, C.: Case of tumor of the right temporosphenoidal lobe bearing on the localization of the sense of smell and the interpretation of a particular variety of epilepsy, Brain 12:346, 1889.

4. Henschen, S. E.: Klinische und Anatomische Beitrage zur Pathologie des Gehirns, ed. 1-6, Uppsala, Almqvist & Wiksell Boktrycheri, 1890-1922.

5. Kennedy, F.: Symptomatology of temporo-sphenoidal tumors, Arch. Int. Med. 8:317, 1911.

6. Cushing, H.: Distortions of the visual fields in cases of brain tumor, Tr. Amer. Neurol. Assoc. 1921, p. 374.

7. Kennedy, F.: In, Discussion on Cushing, H.: Distortion of the visual fields in cases of brain tumor, Tr. Amer. Neurol. Assoc. 1921, p. 374.

8. Horrax, G., and Putnam, T. J.: Distortion of visual fields in cases of brain tumor; the field defects and hallucinations produced by tumors of the occipital lobe, Brain 55:499, 1932.

9. Bender, M. B., and Kanzer, M. G.: Metamorphopsia and other psychovisual disturbances in a patient with tumor of the brain, Arch. Neurol. & Psychiat. 45:481, 1941.

10. Foerster, O.: In, Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Springer, 1936, v. 6, pp. 111, 114.

11. Penfield, W., and Rasmussen, T.: The Cerebral Cortex of Man: A Clinical Study of Localization of Function, New York, Macmillan, 1950.

12. Jolly, F.: Weher Flimmerskatom und Migraine, Berl. Klin. Wchnschr. 39:973, 1902.

13. Pick, A.: The localizing diagnostic significance of so-called hemianopic hallucinations with remarks on bitemporal scintillating scotomata, Am. J. M. Sc. 127:82, 1904.

14. Posey, W. C., and Spiller, W. G., Eds.: The Eye and the Nervous System. Their Diagnostic Relations, Philadelphia, J. B. Lippincott, 1906.

15. Fay, T.: Visual hallucinations in organic diseases of the brain, Arch. Neurol. & Psychiat. 16:377, 1926.

16. Terson, A.: Hallucinations visuelles chez des ophthalmopathes, Ann. d'ocul. 167:815, 1930.

17. Weinberger, L. M., and Grant, F. C.: Visual hallucinations and their neuro-optical correlates, Arch. Ophth. 23:166, 1940.

18. Walsh, F. B.: Clinical Neuro-ophthalmology, ed. 2, Baltimore, Williams & Wilkins, 1957.

19. Schneider, R. C., Crosby, E. C., Bagchi, B. K., and Calhoun, H. D.: Temporal or occipital lobe hallucinations triggered from frontal lobe lesions, Neurology 11:172, 1961.

PSEUDO IRON DEFICIENCY ANEMIA: DIAGNOSTIC SIGNIFICANCE*

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Intelligent appraisal of anemia requires evaluation of red cell hemoglobin content. This may be performed by direct observation of the blood smear for hypochromia or calculation of the mean corpuscular hemoglobin concentration (MCHC). A decrease in the quantity of cell hemoglobin signifies most commonly in the adult, a state of iron depletion resulting from chronic blood loss, much less frequently from an absorbtive defect, or most uncommonly from a dietary deficiency of iron. An even rarer type of primary iron deficiency in young males has been described.[1]

Diagnosis and treatment of true iron deficiency anemia follows a logical sequence of investigation of possible etiologies, correction of the ultimate cause and adequate iron repletion.

Awareness that a similar type of hypochromic anemia may exist in the absence of true iron deficiency is apparently somewhat less wide-spread. A variety of conditions

TABLE I

PSEUDO-IRON DEFICIENCY ANEMIA

1. Thalassemia.
2. Hereditary Hypochromic Anemia.
3. Refractory Hypochromic Anemia
   Responsive to Pyridoxine, nicotinic acid, oral crude liver extract.
4. Chemical Intoxications
   Lead, benzene, fluorine, carbon monoxide.
5. Hypotransferrinemia.
6. Inflammatory-Toxic
   Chronic infection, Chronic inflammation, Malignancy, Uremia.

*Presented in part at The Regional Meeting of The American College of Physicians, Flint, Michigan, December 2, 1960.

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may produce this so-called pseudo iron deficiency anemia and they are listed in figure one. Our principal concern is with the toxic-inflammatory group represented by chronic infectious and inflammatory disease, malignancy and chronic azotemia. Here, the anemia suggesting iron deficiency as indicated by red cell morphology and hypoferremia is belied by the fact that there is no tissue lack of iron, in contrast to the state prevailing in true iron deficiency anemia. Knowledge of this easily obtainable information provides a quick, direct differentiation of pseudo versus true iron deficiency anemia, the practical importance of which may be illustrated by brief reference to the following cases.

CASE ONE: E. R., a 48-year old white male was first seen in November, 1957, with a history of polyarthritis for six months as well as an old history of pulmonary tuberculosis intensively treated and presumably arrested. Physical examination revealed swelling, redness and tenderness in varying combinations of multiple joints consistent with a diagnosis of rheumatoid arthritis. In addition there were pulmonary findings which clinically and by x-ray indicated pleural thickening, apical scarring, multiple areas of fibrosis with large blebs and hydropneumothorax on the left.

In addition to the hematologic data recorded in figure two, the following laboratory data were recorded: Total protein 7.4 gms., albumin 1.5 gms., gamma globulin 3.8 gms. Latex fixation positive. BUN was 15 mgs. %. Up to 40 L E cells were found in the peripheral blood on several determinations. Stool guiac tests were negative.

TABLE II
HEMATOLOGIC DATA

	Case 1 (E.R.)	Case 2 (J.M.)	Case 3 (E.J.)
Hemoglobin	6-7.5 gms	9-7 gms	5-6 gms
MCHC	27%	27%	27%
RBC	Hypo +	Hypo +	Hypo + to ++
WBC	12,700	11,000	4,600
Reticulocytes	1.4%	3.2%	——
Serum Fe	31 mcg. %	——	45 mcg. %
Marrow			
Cellularity	+++	+++	+
Erythroid	Increased	Increased	Normal
Iron	+ to ++	++	++

COURSE: Over the succeeding eighteen months, the patient's arthritis improved on medical management. During this time the hemoglobin returned to a level of 11 to 12 gms. There was, however, gradually increasing dyspnea with death resulting in April, 1959 from pulmonary insufficiency. Post mortum findings were compatible with corpulmonale secondary to pulmonary fibrosis, rheumatoid arthritis, myositis and peripheral neuritis. No definitive evidence of systemic lupus erythematosis or gastrointestinal lesion was found. Likewise there was no evidence of active tuberculosis.

COMMENT: The initial severe hypochromic anemia suggested the possibility of a complicating gastrointestinal cancer. The determination that this was a pseudo iron deficiency on the basis of the marrow hemosiderin, materially dispelled this possibility. The subsequent concomitant improvement of the anemia with the rheumatoid arthritis adequately demonstrated the relationship of these two findings.

CASE TWO: J. M., a 54-year old factory worker entered the Henry Ford Hospital July 2, with complaints of weakness, fatigue, anorexia, alternating diarrhea and constipation plus a 36 lb. weight loss, all occurring over approximately a two month period. He had been seen and treated with digitalis by his local family physician in the preceding month. There was an old history of alcoholism as well as a possible history of acute gouty arthritis in the past. Pertinent history otherwise included nocturia once per night.

Physical examination revealed a chronically ill white male appearing older than his stated age. There was evidence of considerable weight loss, early clubbing of the fingers and palmar erythema. Blood pressure was 130/80. The heart was slightly enlarged. No murmurs were heard and intermittent trigeminy rhythm was observed. Minimal hepatosplenomegaly was present. Initial impressions included probable gastrointestinal malignancy, old Laennec's cirrhosis and probable digitalis intoxication.

Pertinent hemologic data is listed in figure two. Additional laboratory findings included slight proteinuria with increased WBC's and at times RBC's as well as hyaline, granular and occasional WBC casts in the urine. Early in the hospital course, the blood urea nitrogen was 30 mgs.%, serum uric acid 8.7 mgs.%. Complete G. I. series including upper G. I., small bowel, barium enema were negative except for diverticulosis. Proctoscopic examination was negative.

COURSE: Following the first week, the patient began to manifest temperature elevations which subsequently went to as high as 103 degrees. Blood cultures were obtained at this point which revealed streptococcus viridans. At about this same time, definite mitral and aortic valvular murmurs became manifest as well as peripheral petechiae. The patient developed severe thrombophlebitis while on antibiotic therapy and heparin was added to the therapeutic program. Increasing urea retention occurred with a terminal BUN of 177 mgs.%; in addition cardiac failure only partially responsive to therapy, added to the patient's precarious plight. Death occurred on August 18, 1960. Post mortum examination revealed endocarditis of both aortic and mitral valves as well as cerebral hemorrhage.

COMMENT: A hypocromic anemia initially was in keeping with the possibility of chronic blood loss due to a gastrointestinal neoplasm. The finding of normal marrow

content of hemosiderin indicated that this was a pseudo iron deficiency anemia which in turn indicated the possibility of chronic infection; positive blood cultures then substantiated this suspicion.

CASE THREE: E. J., a 19-year old colored female was admitted to Henry Ford Hospital in April, 1960, with the complaints of dizziness, faintness, anorexia and a 7 lb. loss in weight noted over the preceding two months. She had experienced a sore throat with slight fever just prior to admission. There was no history of menorrhagia or other bleeding. Physical examination revealed a young, colored female with evidence of marked pallor of the mucosae and signs of a mild upper respiratory infection. There was a grade II systolic murmur, heard best at the base of the heart. Findings were otherwise negative. Hematologic data are indicated in figure two. Additional laboratory findings included a trace to 1 plus albuminuria with a few hyaline and granular casts, 15 to 25 RBC's and 5 to 7 WBC's on microscopic examination of the urine. Hemoglobin electrophoresis revealed only A hemoglobin. Complete gastrointestinal x-ray examination was negative. BUN was 19 mgs.%, creatinine 1.3 mgs.%. Serology non-reactive. P B I 5.9 micrograms. Total protein was 12.6 gms.; albumin 3.99 gms; gamma globulin 6.5 gms. L E preparations revealed up to 17 L E cells in the peripheral blood.

COURSE: Following institution of steroid therapy the patient has improved subjectively although her anemia remains unchanged.

COMMENT: The severe anemia with hypochromia originally suggested the possibility of a chronic blood loss lesion. The disparity between the level of anemia and the degree of hypochromia as well as the normal hemosiderin content of the marrow, indicated a pseudo iron deficiency anemia. Despite the absence of more characteristic symptoms and findings, the possibility of an underlying systemic lupus erythematosis was proposed and confirmed by additional laboratory data.

DISCUSSION

Although the anemia of chronic inflamatory-toxic diseases is usually no more than moderate in degree as contrasted with the more severe anemia which may occur in true iron deficiency, the evidences of hypochromia, hypoferremia, hypercupremia and elevated erythrocyte protoporphyrin may be entirely similar in the two. The degree of anemia and the tendency to hypochromic-microcytic change in general increases with duration of the underlying disease in this pseudo iron deficiency group. Likewise, marrow findings with respect to erythropoietic hyperplasia and left shift found in the particular group of pseudo iron deficiency anemias under discussion, are not dissimilar from those seen in true iron deficiency anemia. The presence of toxic changes in granulopoiesis as well as non-specific increases in plasma cells and histiocytic elements in the former group are usually of some distinguishing aid.

Since the assessment of iron stores is crucial in the differentiation of true iron deficiency and pseudo iron deficiency anemias, examination of the marrow either microscopically for hemosiderin or chemically for total non heme iron is of fundamental importance. That evaluation of marrow iron is the most reliable and sensitive

diagnostic test for iron deficiency is well documented.[2,3,4] Other procedures such as iron binding capacity, iron tolerance curve, radio iron plasma clearance and red cell uptake are less accurate and more tedious. The method of marrow examination for hemosiderin described by Rath and Finch[5] has been used routinely by us and found to be most satisfactory. Its simplicity and directness allow for an immediate conclusion with regard to the critical question of iron sufficiency. The technique is such that it can be mastered with little effort even by those untrained in hematologic cytology.

Although complete knowledge of the pathogenesis of pseudo iron deficiency anemia is lacking, certain evidences from clinical and experimental observations exist to give some insight into possible mechanisms. The anemia of infection, with changes comparable to that seen in the human, has been studied in various animal experimental models.[6] The counterpart of the hypochromic anemia associated with certain human malignancies has been produced in hamsters by the injection of cell free necrotic material from tumors.[7] The mechanism and effect of the hypoferremia which may be produced by a variety of stress conditions and the implications of the adrenal in this regard, particularly with respect to the latters influence on the reticuloendothelial system, have been studied in some detail.[8] Recent evidence suggests that pseudo iron deficiency anemia as found in infection, rheumatoid arthritis and Hodgkins disease results from a hypoferremia secondary to defective mobilization of iron from senescent red blood cells, following their breakdown in reticuloendothelial cells of the liver and spleen.[9,10,12] The probability that more than decreased serum iron is involved is indicated by the lack of response to continued parenteral iron administration.[11] Moreover, data indicating decreased rate of incorporation of intravenously injected radioiron and marrow evidence of erythropoietic maturation arrest point to decreased marrow function as a cause of the anemia.[12] The best evidence would imply that the defect lies in the insertion of iron into the porphyrin molecule. Electron microscopic studies of erythropoiesis in hypochromic hypersideremic anemias reveal evidence of a blocking mechanism preventing incorporation of iron into the hemoglobin molecule.[13] This probably occurrs in the mitrochondria but the nature of the absent or defective enzyme systems remains to be elucidated.

The diagnostic significance of pseudo iron deficiency anemia presents several aspects. First, its recognition excludes the implications of true iron deficiency and particularly those relating to gastrointestinal diseases associated with occult, chronic blood loss. Futile search for the types of bleeding mucosal lesions which can give rise to a hypochromic anemia may be avoided. In addition, the mistake of ascribing the anemia solely to any gastrointestinal lesion known to be present in the particular case can be safeguarded.

On the positive side, the finding of pseudo iron deficiency anemia requires consideration and systematic exclusion of chronic infectious and inflammatory disease, particularly of connective tissue origin, as well as certain malignancies, notably those of the lymphoma group. Lastly, the possibility of chronic azotemia must be ruled out.

In conclusion, it may be added that as with all dependent medical entities, diagnostic accuracy in this type of anemia allows for a rational direction to therapy based upon discovery and treatment of the underlying disease.

SUMMARY

The morphologic red cell and sideropenic alterations of true iron deficiency anemia may be mimicked by the anemia associated with various chronic inflammatory and neoplastic diseases as well as that found with azotemia. Toxic interference with erythropoiesis occurs in these conditions and results in the production of red cells with decreased hemoglobin content. Unlike the situation which prevails in true iron deficiency anemia, iron stores are adequate; however, some biochemical abnormality induced by the pathologic state prevents the normal incorporation of iron into the hemoglobin molecule.

The diagnostic differentiation of pseudo-iron deficiency anemia and true iron deficiency anemia is most expediently made by evaluation of the marrow iron. The simplified method of examination of unstained marrow particle smears by the method of Finch, lends itself very satisfactorily to this end.

Recognition of pseudo-iron deficiency anemia obviates futile investigations for a source of chronic blood loss. Moreover, awareness of the implications of this entity often provides a clue to the true nature of the underlying disease.

REFERENCES

1. Brumfitt, W.: Primary iron-deficiency anemia in young men, Quart. J. Med. 29:1, 1960.

2. Iron stores and iron deficiency (editorial), Brit. M. J. 1:1167, 1958.

3. McCrea, P. C.: Marrow iron examination in the diagnosis of iron deficiency in rheumatoid arthritis, Ann. Rheumat. Dis. 17:89, 1958.

4. Beutler, E., Robson, M. J., and Buttenwieser, E. A.: A comparison of the plasma iron, iron-binding capacity, sternal marrow iron and other methods in the clinical evaluation of iron stores, Ann. Int. Med. 48:60, 1958.

5. Rath, C. E., and Finch, C. A.: Sternal marrow hemosiderin; method for determination of available iron stores in man, J. Lab. & Clin. Med. 33:81, 1948.

6. Cartwright, G. E., and Wintrobe, M. M.: Anemia of infection; a review, Advances Int. Med. 5:165, 1952.

7. Sherman, J. D.: The relationship of tumor necrosis to red blood cell changes in the hamster, Blood 14:1223, 1959.

8. Gordon, A. S., and Katsh, G. F.: Relation of adrenal cortex to sturcture and phagocytic activity of macrophagic system, Ann. New York Acad. Sc. 52:1, 1959.

9. Weinstein, I. M.: Correlative study of the erythrokinetics and disturbances in iron metabolism associated with the anemia of rheumatoid arthritis, Blood 14:950, 1959.

10. Giannopoulos, P. P., and Bergsagel, D. E.: Mechanism of the anemia associated with Hodgkin's disease, Blood 14:856, 1959.

11. Tótterman, L. E.: Vitamin C and iron metabolism, Acta med. Scandinav. (supp. 230) 134:9, 1959.

12. Freireich, E. J., Miller, A., Emerson, C. P., and Ross, J. F.: Effect of inflammation on the utilization of erythrocyte and transferrin bound radio-iron for red cell production, Blood 12:972, 1957.

13. Bessis, M. C., Breton-Gorius, J.: Ferritin and ferruginous micelles in normal erythroblasts and hypochromic hypersideremic anemias, Blood 14:423, 1959.

A REPORT OF SOME EXAMPLES OF ABNORMAL HALO VOLUME*

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INTRODUCTION

H. V. (halo volume) is the designation given to a peculiar, normal state of selective permeability in the intact bony wall of osteocyte lacunae and the parts of canaliculae close to these lacunae. The permeable zone lies around the lacunae and canaliculae as a three-dimensional halo or cloud.[6,7,11] (See Fig. 1) The selective permeability under normal circumstances is such that simple, inorganic ions can diffuse in limited quantities 2-4 microns into the bony wall of lacunae and canaliculae but larger ions and molecules — on the order of the coal-tar dyes — cannot.[9,11] H. V. permeability disappears both *in vivo* and *in vitro* upon death of the osteocyte normally residing in the lacuna.[9,11] H. V. are stained in perfectly fresh, wet, undecalcified sections properly prepared.[11] Under certain circumstances *in vivo* and *in vitro* enlargement of H. V. is encountered and variations in the morphology of H. V. may be seen.

It has been shown *in vitro* that enlargement in H. V., due to increase in the depth of permeability of the bony wall of the lacunae and canaliculae, occurs in the presence of lowered pH[10] or/and increasing citrate ion concentration.[21] A chemical peculiarity of the organic matrix in the H. V. part of bone has also been shown.[22]

What does this zone of selective permeability mean?

For years it has been suspected that osteocyte metabolism exerts some effect on the exchange of inorganic substances between bone and blood.[9,16,17,19] Some work indicates that the path of pyruvate and Kreb's cycle metabolism is abnormal in bone.[1,2,13,17,20,22] This work also suggests that parathormone and vitamin D or vitamin D analogs are in some way involved in the abnormality. The presence of an abnormality in osteocyte metabolism should be detectable if the proper methods for detection were available. It may be that H. V. abnormalities reflect the disturbances in pyruvate and Kreb's cycle biochemistry already referred to. If so, H. V. study is one route open for studying these biochemical activities of osteocytes.

Even if H. V. abnormality is eventually found to be related to other aspects of metabolism than those referred to,[15] a report of cases in which detectable abnormality occurred is warranted. Such a report focuses attention on a basic problem — osteocyte metabolism — and indicates the need for more work and thought on this problem.

In this paper we report some instances of H. V. abnormality detected in several human cases either on biopsy material or an autopsy material.

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METHODS

Fresh, undecalcified sections were made.[5] Fuchsin stained sections were made from every case.[6] Special H. V. stains by a boiling permanganate technique were done in 3 cases.[6,11]

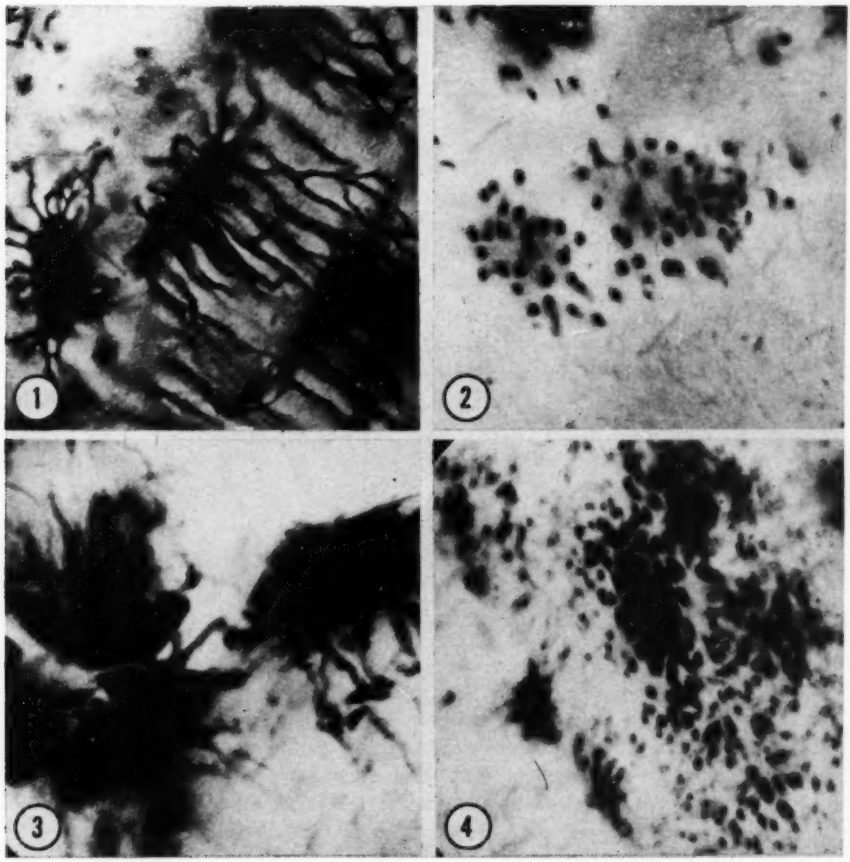

Figure 1

Undecalcified, fresh, undehydrated sections human bone.

(1) and (2) are oil immersion views of a lacuna and its canaliculae in longitudinal and cross section respectively. Stained with boiling basic fuchsin. The apparent size of the structures closely resembles the real size. About 2000 X.

(3) and (4) are similar views of lacunae and canaliculae in another section of the same bone, but stained with boiling permanganate. The magnification is the same as in (1) and (2). The apparent increased thickness of lacunae and canaliculae is the result of penetration of permanganate into the walls of the lacunar and canalicular lumens.

The walls are thus permeable to small, but not large, ions. This permeability and its selectivity constitute halo volume.

It must be understood that there are two degrees of abnormally large H. V. In the case of mild enlargement, detection may be achieved only with simple inorganic ions and such enlargement is not accompanied by microradiographic abnormality. In the case of severe enlargement, detection may be made by staining even with very large molecules, and in these cases there is a corresponding and obvious decrease in density on microradiographs provided the resolving power of the microradiographic equipment is adequate (better than about 3 microns), and sections are not too thick (under 15 microns).

Normal H. V. are illustrated in Fig. 1.

It is understood that the size of the selective permeability demonstrated by the various staining procedures is limited by *in vitro* factors such as staining time, temperature and so on. The actual, "biological" size of the readily permeable zone during life may be quite different from that shown on the various illustrations accompanying this article. The demarcation between H. V. bone and non-H. V. bone may also be artificially sharp on these illustrations. It is most likely that permeability varies gradually rather than abruptly in a single moiety of bone.

The 4 cases presented here are part of the 515 cases (as of this writing) that have contributed over 1400 bones to the Henry Ford Hospital Orthopaedic Research Laboratory. Fresh, undecalcified, fuchsin-stained sections have been made from all of these cases. Permanganate H. V. stains have been done on about 100 of them. These figures are quoted first, to indicate that the laboratory's experience with human bone is more than casual and second, to indicate the frequency of the abnormalities which will be presented.

CASE REPORTS

(1) C. M.,* 11 yr. WM. Diagnosis of Albers-Schonberg's disease by X-ray. Two biopsies of the femoral cortex obtained at intervals of two months. The bone biopsied was the normal, circumferential lamellar collar surrounding the chondro-osseous complex. (See Fig. 2)

This patient came under observation during routine chest X-ray screening.

The following values were normal in this case: urea nitrogen, total serum protein and A/G ratio, serum uric acid, serum calcium and phosphorus, cephalin flocculation, thymol turbidity, urine Sulkowich, WBC and differential. The alkaline phosphatase was 10.2 Bodansky units, the acid phosphatase 1.5 G.G. units, the P.S.P. excretion after 2 hours varied between complete excretion to 67% excretion. Hemoglobin was 10.2 gm% - 12.5 gm%. Hematocrit 40%.

As Fig. 2 reveals, there are large numbers of fuchsin permeable and enlarged halo volumes in the bipsy specimens. This feature is seen on both biopsies but is most prominent in the first one.

(2) J.R., 14 WM. Congenital ureteral obstruction with hydroureter and hydronephrosis. Repeated, prolonged urinary tract infections. Died 1960 in uremia. Specimens: distal third of tibia, one rib, obtained at postmortem. Kept in formalin for 24 hours before sectioning.

*From the House of St. Giles the Cripple, Brooklyn, N. Y.

Figure 2

Cross section, undecalcified, basic fuchsin, about 1500 X, 11 year old boy with osteopetrosis. The specimen is a biopsy from the lateral femoral cortex, M/3. Radiographically this was an area of lamellar bone; histologically it was also lamellar bone.

Near the center of the plate are a group of osteocyte lacunae that are surrounded by halos of fuchsin-stained bone. To have a fuchsin halo the bone around the lacunae must be incompletely mineralized.

No permanganate stain done on this case. Biopsy specimen prepared and stained fresh.

Note that the halo affects the perilacunar bone more than the pericanalicular bone.

Laboratory data: serum Calcium 8.5 mg%; serum PO_4 11.2 mg%; NPN 100; urea nitrogen 60-70 mg%. Alkaline phosphatase 12.8 Bodansky. Creatinine 4.2 mg%. The boy was dwarfed, had secondary rickets, was pale, underweight, had a protruberant abdomen, duplication of the epiphyses and a rachitic rosary. Fig. 3 reveals the rachitic changes in the distal tibial and fibular epiphyses.

Figure 3

X-rays of Case (2) revealing rachitic changes in distal tibial and fibular epiphyses. Widening and irregularity of the plate are present.

In Fig. 4 photomicrographs of this patient's tibia may be seen. The numerous and enlarged, fuchsin-permeable halo volumes are well displayed. This patient had parathyroid hyperplasia, the parathyroid glands being enlarged and massive osteoclastic activity being present in the bone sections.

(3) I.K.; 9 WM[9] - so-called vitamin D resistant rickets, actually renal phosphate diabetes. Dwarfed, severe clinical and radiologic manifestations of clinical rickets; positive family history. Typical laboratory data: alkaline phosphatase 16 Bodansky units; serum calcium 9 mg%; serum PO_4 2.0 mg%; 24 hour urinary amino acid nitrogen 73 mg; renal tubular phosphate reabsorption 73%.

The patient was free of all vitamin D or vitamin D analog treatment 8 weeks prior to operation for correction of severe bowing of the legs. The resected pieces of bone comprised the specimens examined.

In Fig. 5 the large, fuchsin permeable halo volumes present in this case may be seen. It should be noted that microradiographs of other cases of this disease reveal the same defect in mineralization in the shell of bone enveloping the osteocytes that is revealed here. In other words, this finding is not unique in this case but appears to be a typical feature of the disease. Of incidental note is that the sections revealed evidence of severe rickets: numerous, thick osteoid seams, much low density bone.

(4) J.K.; 58 WM;[4] Patient has an unusual and bizarre trabecular pattern in the bones of the axial skeleton. (See Fig. 6). Extensive clinical laboratory studies were normal and include fecal calcium, renal tubular phosphate reabsorption, renal

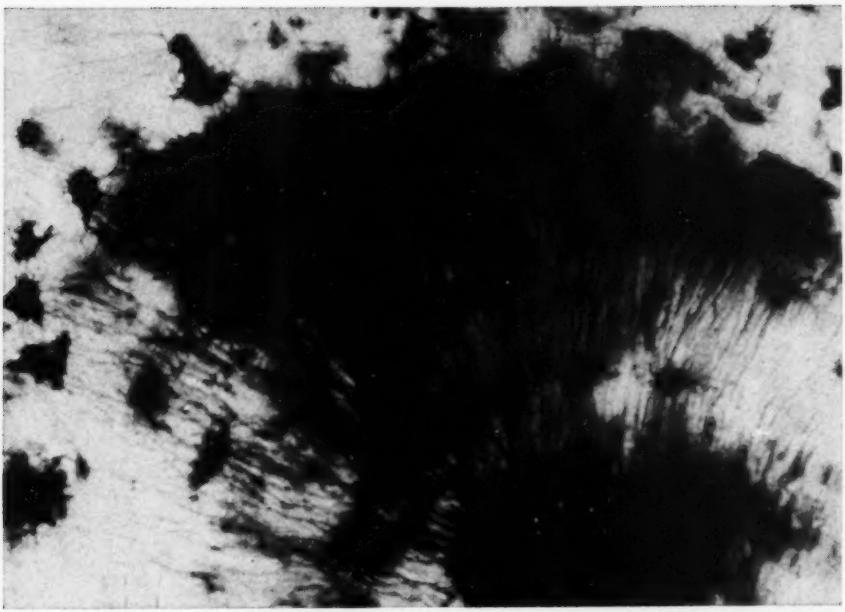

Figure 4

Undecalcified cross section D/3 tibia, basic fuchsin of boy with Uremia, secondary rickets. At the lower right is an Haversian canal in cross section. Near the top are a group of lacunae surrounded by fuchsin halos. The halos are accentuated in all these photomicrographs through use of appropriate filters when taking the original photos.

Above the group of affected lacunae is a narrow strip of additional undecalcified bone containing normal lacunae. This "spotty" distribution of abnormal H. V. seems to be the rule in pathological material. Material obtained at autopsy.

function, CBC, serum calcium and phosphorus serum acid and alkaline phosphatase, serum bilirubin, FBS and urea nitrogen. An iliac crest biopsy reveals severe feathering and an excess of osteoid seams. A permanganate halo volume stain done on a part of the fresh biopsy specimen reveals enlarged halo volumes. (See Fig. 7). This is one of three other similar cases reported to the American College of Physicians, Miami, May, 1961 by Frame, Ormond, Frost and Hunter. This patient was initially seen and X-rayed for a cervical radiculitis, and in this respect is similar to the other 3 cases.

DISCUSSION

It has been suggested elsewhere that the abnormal halo volume seen in vitamin D resistant rickets (or renal phosphate diabetes) is a characteristic feature of this disease.[8] In the present case there was no treatment with vitamin D or its analogs for at least 8 weeks prior to the osteotomies from which the biopsy material was obtained. This seems to rule out an effect of vitamin D on osteocyte metabolism as a cause of the observed abnormality. We are left with the suggestion that a disturbance in osteocyte metabolism is one of the features of this disease. It has been pointed out

Figure 5

Undecalcified, fuchsin-stained cross section fibula from 9 year old boy with vitamin D refractory rickets. Part of an Haversian system is seen at the right; the Haversian canal is lined with an osteoid seam.
In the center of the figure osteocyte lacunae may be seen. Some of these lacunae are accompanied by a fuchsin halo. The halo is unusual, in that it seems to be always on one and the same side of the lacunae. This is the side containing the majority of the canaliculae and indicates that here there is an abnormal canalicular rather than lacunar halation.
Material obtained fresh from operating room.

Figure 6A

A lateral view of cervical spine of 58 year old man with bizarre, anarchic trabecular pattern in most of the bones of the axial skeleton and in none of the bones of the appendicular skeleton or skull.

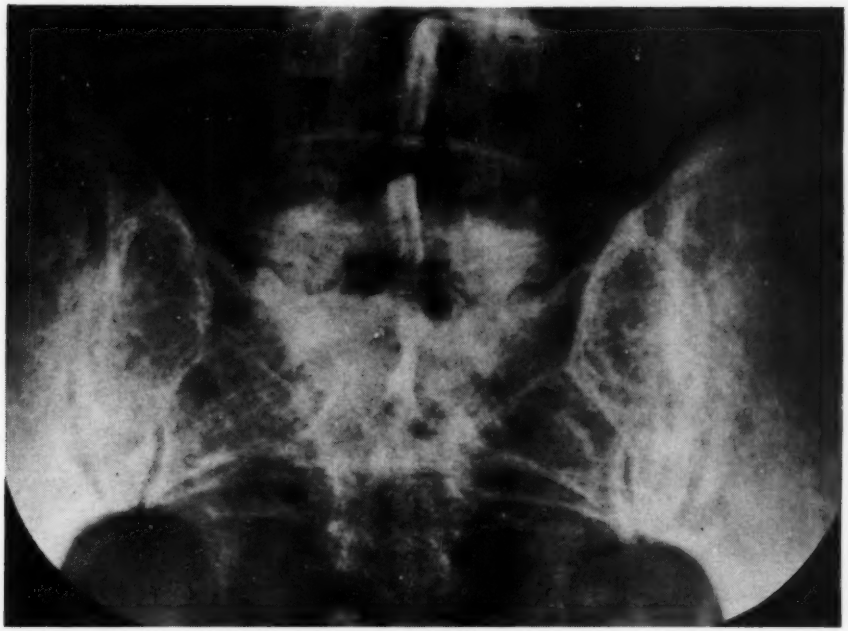

Figure 6B

A-P view of L-S junction region in same case as in 6A. There is less anarchy in trabecular orientation here but the trabeculae are irregularly thickened.
Four of these cases are being separately reported.

elsewhere why the observed abnormality cannot be explained on the basis of disturbed serum chemical values.[8]

On the basis of morphology it would appear that the halo volume disturbance in the case of vitamin D resistant rickets is the result of a different metabolic abnormality in the osteocyte than is the case in the other three patients presented. In other words, our illustrations are compatible with the presence of at least two different osteocyte metabolic disturbances. It is understood that while this is suggested, it is not established.

Various theories of parathormone action have been proposed in which the central idea is that parathormone in some manner stimulates the formation of large amounts of citrate by osteocytes.[17,20] If such were the case, it would logically be possible that removal of some of the calcium from the bony wall around the osteocytes would occur and lead on undecalcified sections to an enlarged halo volume.[21] This attractive theory, proposed by the Neumanns[17] and Nordin,[20] is unproved. At first glance our boy with parathyroid hyperplasia would seem to be a confirmatory case. This is brought up, however, to discourage the idea. There are three other cases of hyperparathyroidism in the Research Laboratory's files and none of them exhibit a similar disturbance. All are adults, however, and as Jaffe has observed,[12] the age of the

Figure 7

Permanganate stain of fresh, undecalcified iliac crest biopsy specimen obtained from case (4) of test; same patient as in Figures 6A, 6B.

The numerous small dark blotches represent permanganate stained, enlarged H. V.; the much larger, darkened areas are permanganate-stained feathered bone.

In this man it is necessary to make the provocative observation that he (and the 3 similar ones being reported with it) has no clinical illness to relate with the x-ray and histologic abnormalities.

individual affects the manner in which he responds to excess parathormone. Accordingly, either the case in the present study is an example of parathormone effect in a child, or the abnormal H. V. are the result of some other biochemical disturbance than one in the Kreb's cycle.

At present there are no grounds which would permit us to attempt identification of the metabolic disturbance in the osteocytes in the four cases reported, although there are some possibilities to explore. We cannot even postulate why only some of these cells display the abnormality rather than all of them. There obviously is room for a great deal of work in this area.

SUMMARY

Four cases are presented, drawn from among 515 in the files of the Henry Ford Hospital Orthopaedic Research Laboratory, in which a morphological disturbance in halo volume is present. Halo volume is a state of selective permeability in the bony wall of lacunae containing living osteocytes. Enlargement of halo volume to an abnormal degree is considered suggestive of a disturbance in the metabolism of the osteocyte. The exact nature of this disturbance is unknown.

REFERENCES

1. Borle, A. B., Nichols, N., and Nichols, G., Jr.: Metabolic studies of bone *in vitro*. I. Normal bone, J. Biol. Chem. 235:1206, 1960.

2. Dixon, T. F., and Perkins, H. R.: Citric acid and bone metabolism, Biochem. J. 52:260, 1952.

3. Engfeldt, B., Zetterstrom, R., and Winberg, J.: Primary vitamin D resistant rickets. III. Biophysical studies of skeletal tissue, J. Bone & Joint Surg. 38A:1323, 1956.

4. Frame, B., Ormond, R., Frost, H. M., and Hunter, J.: Axial osteomalacia, Presented before the Annual Meeting of the American College of Physicians, Miami, May 1961.

5. Frost, H. M.: Preparation of thin, undecalcified bone sections by a rapid manual method, Stain Technol. 33:273, 1958.

6. Frost, H. M.: Staining of fresh, undecalcified thin bone sections, Stain Technol. 34:135, 1959.

7. Frost, H. M.: Biophysical characteristics of bone, Presented before the Orthopedic Research Society, Chicago, January, 1957.

8. Frost, H. M.: Some observations on bone mineral in a case of vitamin D resistant rickets, Henry Ford Hosp. M. Bull. 6:300, 1958.

9. Frost, H. M.: Some aspects of the mechanics and dynamics of blood-bone interchange, Henry Ford Hosp. M. Bull. 8:36, 1960.

10. Frost, H. M., Roth, H., Villanueva, A. R.: Halo volume. I. Effect of pH on size, Henry Ford Hosp. M. Bull. 9:126, 1961.

11. Frost, H. M., Roth, H., and Villanueva, A. R.: Halo volume, Henry Ford Hosp. M. Bull. 8:228, 1960.

12. Jaffe, H. L., Bodansky, A., and Blair, J. E.: The influence of age and of duration of duration of treatment on the production and repair of bone lesions in experimental hyperparathyroidism, J. Exper. Med. 55:139, 1932.

13. Kenny, A. D., Draskóczy, P. R., and Goldhaber, P.: Citric acid production by resorbing bone in tissue culture, Amer. J. Physiol. 197:502, 1959.

14. MacGregor, J., and Nordin, B. E. C.: Equilibration studies with human bone powder, J. Biol. Chem. 235:1215, 1960.

15. McConnell, D., Frajola, W. J., and Deamer, D. W.: Relation between the inorganic chemistry and biochemistry of bone mineralization, Science 133:281, 1961.

16. McLean, F. C.: The ultrastructure and function of bone, Science 127:451, 1958.

17. Neuman, W. F., and Neuman, M. W.: Chemical Dynamics of Bone Mineral, Chicago, University of Chicago Press, 1958.

18. Basset, C. A. L., and Nordin, B. E. C.: The "Calcium-phosphate product" in an *in vitro* system of surviving bone, Acta Orthop. Scand. 28:241, 1959.

19. Nordin, B. E. C.: Personal communication.

20. Nordin, B. E. C., and Fraser, R.: Indirect assessment of parathyroid function, In, Ciba Foundation Symposium on Bone Structure and Metabolism, ed. by G. E. W. Wolstenholme, and C. M. O'Connor. Boston, Little Brown, 1956, p. 222.

21. Roth, H., Frost, H. M., and Villanueva, A. R.: Halo volume. II. Effect of citrate ion concentration on size, Henry Ford Hosp. M. Bull. 9:130, 1961.

2. Van Reen, R.: Metabolic activity in calcified tissues: Aconitase and isocitric dehydrogenase activities in rabbit and dog femurs, J. Biol. Chem. 234:1951, 1959.

23. Villanueva, A. R., Frost, H. M., and Roth, H.: Halo volume. III. Existence of a pattern in the matrix, Henry Ford Hosp. M. Bull. 9:133, 1961.

PREMATURITY AND NEUROLOGICAL DISORDERS*

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JOHN A. CHURCHILL, M.D.**

INTRODUCTION

Prematurity has long been considered to be a handicap in respect to both motor and mental development. The purpose of this paper is to show the relationship of prematurity to various neurological disorders of obscure etiology, such as, mental deficiency, epilepsy, and cerebral palsy. In this study prematurity is considered to be present when the birth weight of a given infant was fewer than 2500 grams and the gestational age was fewer than 40 weeks. It has already been shown that prematurity is a highly significant factor in spastic diplegia, to such an extent as to indicate a causual, though not necessarily direct, relationship between prematurity and the disease.[1] There is an association between prematurity and mental deficiency if a premature infant is defined as one weighing fewer than 2500 grams at birth. However, if the criteria of prematurity are based on gestational age as well as birth weight, the association of prematurity with mental deficiency is obscure.

METHOD OF PROCEDURE

We wished to inquire further into the relationship of prematurity to other neurological disorders. In the present study the cases in the cohort were assigned to one of the following series on the basis of their clinical manifestation:

1. Cases with I.Q. over 90, physically and neurologically negative, but may have headache or various psychological or behavioral disorders.
2. Cases with mental deficiency (I.Q. below 70) as the sole problem.
3. Cases with mild mental deficiency (I.Q. 70 to, and including 89) as the sole problem.
4. Deafness with or without mental deficiency.
5. Mental deficiency with seizures.
6. Convulsive states. The series of convulsive states was originally considered with regard to the three separate conditions; seizures, type undetermined, "idiopathic" epilepsy, and focal cerebral seizures. It was apparent from our statistical data that prematurity was not a significant factor in any of these three groups and was no more significant in any one than the other two conditions. These three disorders were then grouped together for statistical comparison with the normal series.
7. Hemiplegic cerebral palsy, with or without seizures.

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**Division of Neurology.

8. Spastic diplegic cerebral palsy.
9. Complex diplegic cerebral palsy.
10. Athetoid cerebral palsy.
11. Hyperkinetic impulse disorder.

Over the past five years the authors have made a systematic collection of data regarding the factors of gestation and delivery of all children brought by their mothers for neurologic consultation. Histories were obtained item for item in the same manner in all cases, regardless of the presenting complaints. Requests for prenatal and perinatal histories were sent to the hospital of birth. Information was obtained from approximately 15% of the cases. The majority of the patients came from middle income families in Detroit and its environs. As a group, the mothers of these children were intelligent, interested in the welfare of their children, and were quite well informed regarding prenatal care and child health. None were deprived of the means to obtain adequate diet or necessities of life. All but eleven children in the entire cohort were born in this hospital. To determine the magnitude of error in histories, a determination of concordance between the mother's history and hospital records was made in regard to birth weight and gestational age in those cases where hospital records were obtained. This was done in cases with mental deficiency, epilepsy and spastic diplegia. Hospital records were available in 37 cases of mental deficiency and of these discordances between the mother's history and hospital record in regard to birth weight occurred in only 2 (5%). Hospital records were available in 80 cases with epilepsy. In this group discordances were observed in 10 cases (13%). Hospital records were available in 16 cases with spastic diplegia. In this group, discordance was observed in one case (6.25%). The average age of the patients with mental deficiency when first seen was 4.5 years, the average age of the patients with epilepsy was 8.0 years, and the average age of patients with spastic diplegia was 4.8 years. The discordance between the mother's history and hospital record in the mental deficiency series, the epilepsy series, and the spastic diplegia series could be attributed to errors in recall due to lapse of time. Nevertheless, it should be apparent that the discordances were minor. In respect to the concordance of hospital and mother's history concerning gestational age, the series of cases with mental deficiency had a discordance rate of 10%, the epilepsy series a discordance rate of 13%, and the spastic diplegia series a discordance rate of 6.25%.

Each patient was subjected to a systematic neurologic examination. The findings were recorded on data collection forms at the time of examination. Psychometric tests performed by a psychologist who did not know the patient's birth history or about this work, were obtained in most of the patients who were suspected of having mental deficiency. Psychometric tests were not obtained in some of the severely defective and in many of the obviously normal children.

ANALYSIS OF DATA

The cohort totaled 1245 cases. There were 212 in the neurologically normal group, including 13 (6.1%) prematures. There were 17 (8.1%) prematures in 191

mental deficiency cases, 3 (7.3%) prematures in 41 mild mental deficiency cases, 10 (29%) prematures in 34 cases of deafness with or without mental deficiency, 8 (18%) prematures in 45 cases of mental deficiency with seizures, 29 (7.3%) prematures in 398 cases of convulsive states, 11 (12.4%) prematures in 89 cases of hemiplegic cerebral palsy, 64 (78%) prematures in 82 cases of spastic diplegic cerebral palsy, 14 (16.3%) prematures in 86 cases of complex diplegic cerebral palsy, 6 (13.0%) prematures in 46 cases of athetoid cerebral palsy, 2 (9.5%) prematures in 21 cases of hyperkinetic impulse disorder. The Chi square test was carried out to determine the statistical significance of the numbers of prematures in each group. As shown in Table I, the Chi square was significant, that is, P was less than .001, in the two series, deafness with or without mental deficiency and spastic diplegic cerebral palsy. The mean weight of each series and the mean weight of the prematures in each series are shown in Table I.

There is a significantly high incidence of prematurity in the series of cases of deafness with or without mental deficiency (P is less than .001). A series of 39 deaf children has been previously reported, of whom 9 (23%) had birth weights under 2500 grams.[2]

Figure I compares with I.Q.'s of 64 premature spastic diplegic cerebral palsy cases to an I.Q. curve such as would be found in the general population. Statistical comparison of the I.Q.'s of the premature spastic diplegic cerebral palsy group and of the general population was done by the analysis of variants technique, where the variance ration, F="between" mean square/ "within" mean square, gives the following result: $F=22.2, u_1=1, u_2=3246$. From this, P is far less than .001.

DISCUSSION

This study shows again that there is a very strong association between prematurity and spastic diplegia. There is no demonstrable association, however, between prematurity and mental deficiency or epilepsy in our case material. If we consider prematurity on the basis of birth weight only, then there is correlation between prematurity and mental deficiency. This correlation disappears when we consider gestational age as well as birth weight in defining prematurity.

It is interesting that the mean weight of the prematures in the mental deficiency series is significantly higher than the mean weight of the prematures in the spastic diplegia series (2213 as compared with 1520 grams); and is also higher, though not significantly so, than the mean weight of the prematures in the normal group (2009 grams).

We find a correlation between prematurity and deafness with or without mental deficiency, but no evidence as to the etiology of these conditions is suggested from this study.

The I.Q. distribution of our 64 premature spastic diplegia cases has been statistically compared to the I.Q. distribution found in the general population, and has been found to vary significantly, although not greatly, from the expected norm. It must

Table I

Comparison of Series with Different Neurologic Disorders

to a Neurologically Normal Series in Regard to Prematurity

SERIES	Cases	Premature	Percent Premature	Chi Square	P less than .001	Mean weight of Series	Mean weight of Prematures in Series
Normal	212	13	6.1	——	——	3242	2009
Mental Deficiency	191	17	8.9	.66	0	3000	2125
Mild Mental Deficiency	41	3	7.3	.29	0	3145	2291
Deafness (With or without M.D.)	34	10	29.0	18.74	+	2611	1775
M.D. + Sx	45	8	18.0	2.99	0	3081	2094
Convulsive States	398	29	7.3	.29	0	3223	2002
Hemiplegia	89	11	12.4	3.31	0	3220	1875
Spastic Diplegia	82	64	78.0	70.71	+	1863	1520
Complex Diplegia	86	14	16.3	7.65	0	2978	2054
Athetoid	46	6	13.0	2.65	0	3065	1947
Hyperkinetic	21	2	9.5	.36	0	3137	2000
Total	1245	177	14.2				

be remembered too that psychometry of children with cerebral palsy is difficult, as these children with impairment of motor function cannot readily explore their environment, and they have difficulty communicating with others. The values shown indicate again that even very early prematurity is not strongly associated with mental deficiency.

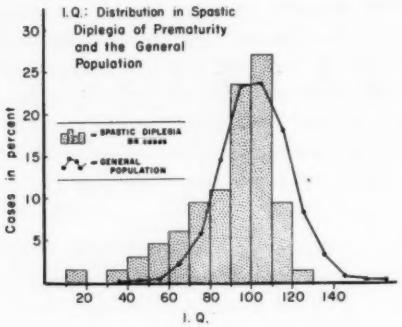

Figure 1

We have a series of seven cases of triplegic cerebral palsy. This series, however, was not included in Table I as the number was too small to be statistically significant. All of these seven cases were premature (mean birth weight 1518 grams). We believe that these seven cases had spastic diplegia of prematurity initially with the subsequent onset of hemiparesis, resulting in triplegia.

SUMMARY

When the criteria for prematurity are (a) gestational age of fewer than 40 weeks and (b) birth weight of fewer than 2500 grams, this study indicates the following:

1. Spastic diplegic cerebral palsy is strongly associated with prematurity.
2. Deafness with or without mental deficiency is strongly associated with prematurity.
3. Mental deficiency is weakly if at all associated with prematurity, but is associated with full term (i.e. 40 week gestational age) children with birth weight fewer than 2500 grams.
4. Epilepsy is not associated with prematurity.

REFERENCES

1. Churchill, J. A.: Relationship of Little's disease to premature birth, A.M.A. J. Dis. Child. 96:32, 1958.

2. Johnsen, S.: Natal causes of perceptive deafness, Acta oto-laryng. 42:51. 1952.

SOLITARY PULMONARY METASTASIS FROM HYPERNEPHROMA NINE YEARS FOLLOWING SURGERY

R. E. REINHARD, M.D.*

Long term survival following nephrectomy for hypernephroma is not common. In one study it was found that 19.5% of patients with proven hypernephroma were alive at the end of ten years; only 9.08% were free from tumor at the end of a ten-year period.[1] Although there has been mention in the literature of patients who have survived twenty years or longer, these cases were uncommon.[2,3,4]

A 66-year old white male was first admitted to the Henry Ford Hospital in 1952 with right flank pain and microscopic hematuria. A retrograde pyelogram demonstrated a tumor deformity of the right kidney (Figure 1). There was no evidence of metastatic disease. Surgical exploration revealed a tumor in the lower pole of the kidney. The microscopic diagnosis was clear cell carcinoma (Figure 2). "The cell type of this tumor is a large vacuolated cell, having clear cytoplasm and distinct cell borders. The nucleus is moderately small in comparison to the size of the cell. It is oval and eccentricly placed. The cells tend to group themselves, and are surrounded by a moderately thickened stroma which presents much the appearance of a honeycomb. There are some rather large strands of fibrous trabecular running throughout the growth." Of the various histologic types, these reportedly have the best prognosis.[5]

Following surgery, no irradiation was given and the patient remained asymptomatic. Interval examinations failed to reveal evidence of recurrence.

This patient was again admitted to the hospital in 1961 for surgical exploration of an enlarging lesion in the lingula of the left lung. He denied pulmonary symptoms. This lesion was noticed on a routine chest x-ray (Figure 3). Positive physical findings were a left inguinal hernia, varicose veins, and mild hypertension. Routine laboratory studies were within normal limits. X-rays of the left knee revealed cystic areas in the upper tibia and fibula, which were interpreted as being benign. A recent I.V.P. showed a normal left pyelogram. The patient was explored through a left thoracotomy incision, and a neoplasm was found in the superior portion of the lingula. A left upper lobectomy was done. The patient's postoperative course was satisfactory, and he was well when last seen. The microscopic diagnosis was metastatic renal carcinoma (Figure 4). "The tumor is composed predominantly of clear cells arranged in diffuse sheets and in solid alveolar masses. The cells are cuboidal and have a well defined clear cytoplasm. The nuclei are small, round, and deep staining. This tumor has essentially the same structure as the original hypernephroma."

DISCUSSION

Metatases occurring several years after resection of the primary lesion are most of the kidney most commonly metastasizes to bone, lung, and brain. However commonly seen in carcinoma of the thyroid, occasionally in carcinoma of the breast, ocular and cutaneous melanoma, and hypernephroma. It has been found that carcinoma

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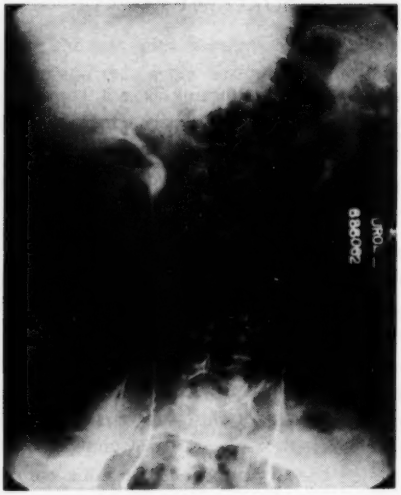

Figure 1

Retrograde Pyelogram of the Right Kidney Showing Tumor Deformity.

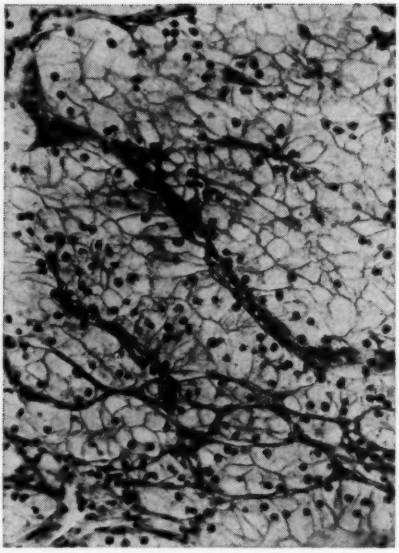

Figure 2

Microscope Examination Showing Clear Cell Carcinoma.

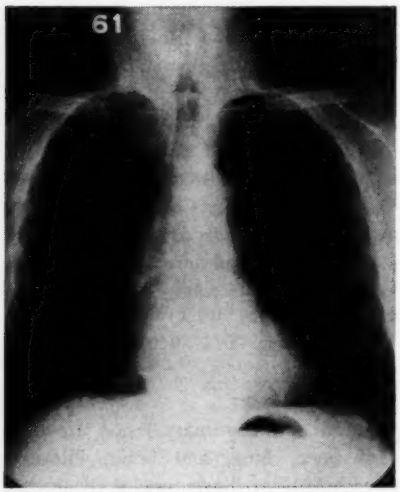

Figure 3

Chest X-ray 9 years after Operation Showing Lesion in Lingula on Left Side.

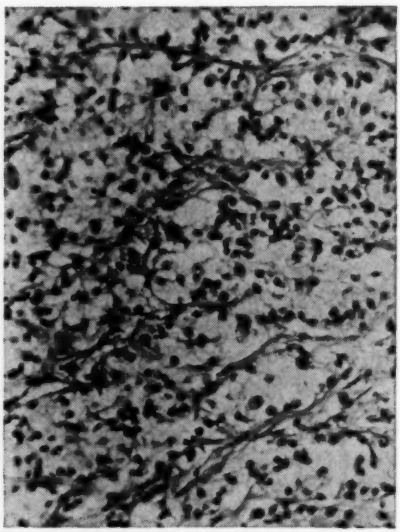

Figure 4

Microscopic Examination again Showing Clear Cell Carcinoma.

metastases may be found in the gallbladder, bile ducts, skin, corpus cavernosum, epididymis, intestine, pancreas, thyroid gland, pericardium, heart, mediastinum, seminal vesicles, mouth, external auditory meatus, and phalanges. Metastases from hypernephroma may occur in only one organ. Those in the lung may occur as single nodules or cotton wool patches.[2]

In our patient, no evidence of metastatic disease was present until nine years following the initial surgery. As far as we are able to determine, this represents a solitary metastasis.

SUMMARY AND CONCLUSIONS

A patient with a solitary lung metastasis from a hypernephroma nine years following nephrectomy is presented. Because of the sometimes erratic behavior of these tumors, close follow-up is recommended.

REFERENCES

1. Deming, C. L.: Prognosis and problems in renal tumors, J. Urol. 55:571, 1946.

2. Rosof, B. M., and Rubin, R.: Metastasis from hypernephroma twenty years after nephrectomy: report of a case, J.A.M.A. 173:896, 1960.

3. Graves, R. C., and Mabrey, R. E.: Adenocarcinoma of kidney recurrent after twenty years, New England J. Med. 212:416, 1935.

4. Starr, A., and Miller, G. M.: Solitary jejunal metastasis twenty years after removal of a renal-cell carcinoma: report of a case, New England J. Med. 246:250, 1952.

5. Foot, N. C., Humphreys, G. A., and Whitmore, W. F., Jr.: Importance of accurate pathological classification in prognosis of renal tumors, J. Urol. 61:477, 1949.

A METHOD OF ORTHOGRAPHIC PROJECTION FOR DELINEATING AND MEASURING GROSS SPECIMENS

WM. E. LOECHEL*

There are frequent occasions when a gross specimen or a series of specimens present extremely valuable details which are easily appreciated when the object can be handled and examined but which seem to defy concise representation when drawn in two dimensions for publication. To sketch such subjects is time consuming and is not accurate to the degree that one might wish. In addition, one's final product is a three dimensional appearing subject, complete with perspective which is definitely not wanted in these instances. The same is true of the photographic effort, especially if the surface is large and receding or if there are several areas in the depth of the single subject that should receive attention.

The author first met with this problem while attempting to produce brain maps and topographical studies of the Sylvian fissure. A relatively simple solution was found which would allow any point (or area) to be delineated as a direct projection upon a common flat surface. The accompanying sketches show the method of delineation. One has simply to position the subject as he wishes and support a piece of thin picture glass above it, as close to the surface of the specimen as possible, being careful to see that the glass is in a plane parallel to the one upon which the specimen rests. After sighting through (or lining up) the two etched points, a fine pen is used to make a small dot on the glass. By continuing to sight and mark, the entire course or contour of the subject will be plotted. If all is correctly aligned, the end result will be a full scale projection of the subject.

Artistic talent is not a requisite; one has only to fix the axes and planes of his specimen and glass and the delineation becomes automatic. The mark made by the pen should not be visible until the "sight" is moved to the next step along the line. Results are often surprising; this type of delineation is the mechanism for removing the natural tendency to see perspective.

The completed drawing on the glass plate can be traced on suitable paper for publication.

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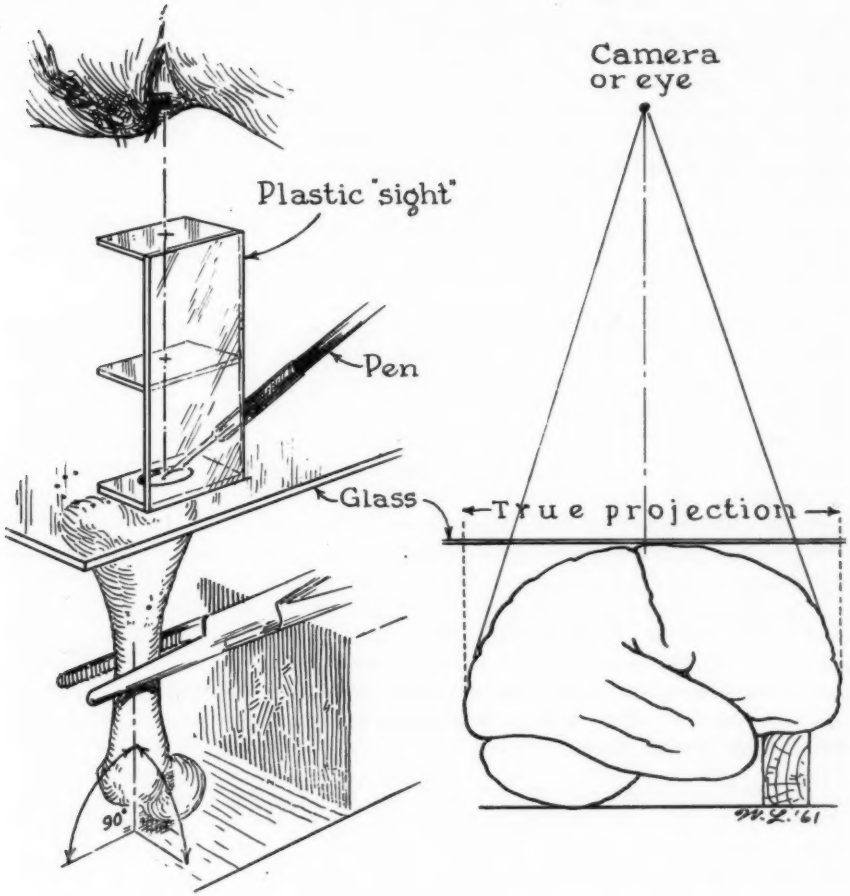
*Director, Medical Illustration Department



Apparatus for orthographic projection

ETIOLOGY OF JUVENILE HYPERTHYROIDISM*

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The last two decades have witnessed significant advances in the laboratory diagnosis and treatment of hyperthyroidism in children. Kennedy and his group[1,2] have written extensively on this subject, covering all facets with emphasis on the results of surgery. Wilkins, Van Wyk *et al*[3] recorded their experiences with thiourea drugs, pointing out that satisfactory results can be obtained in a large percentage of cases when treated for two or three years. Arnold *et al*[4] critically evaluated the advantages and disadvantages of the medical approach as compared to surgery. Their conclusions favor the latter as offering equal expectation of "cure" with less impact on the patient and the family. The purpose of this paper is to present a new postulate for the etiology of hyperthyroidism, tabulate data obtained from hospital case records and determine whether the postulate correlates with the data.

The etiology and pathogenesis of hyperthyroidism are still unknown. A completely successful treatment must eliminate or at least control the causative factor. Accordingly, it was decided to re-examine the current thinking on etiology. Li *et al*[5] showed that Protein Bound Iodine (PBI) and I^{131} uptake are reduced to hypothyroid levels following hypophysectomy in man. Moschcowitz[6] observed that thyrotoxic patients represented a form of neuro-circulatory asthenia upon which hypermetabolism was superimposed. The same personality remained after remission of the thyrotoxic symptoms. Thompson[7] felt that "exophthalmic goiter develops as a result of a complex chain of events involving the thyroid, anterior lobe of the pituitary and the hypothalamus". Canary and his group[8] used reserpine to combat a possible diencephalic disturbance in conncetion with Graves' disease. The patients were clinically improved, but the PBI and the I^{131} uptake remained in the hyperthyroid range. These articles point out: 1) That normal thyroid function depends upon an intact hypothalamic-pituitary-thyroid axis. 2) That hyperthyroidism occurs in patients with an unstable nervous system. 3) That hyperthyroidism is characterized by an interference with normal hypothalamic control.

Werner[9] has shown that the increased I^{131} uptake of hyperthyroidism is not suppressible by exogenous thyroid. Becker[10] reported two cases of hyperthyroidism in whom hypophysectomy did not lower the PBI or the I^{131} uptake. McCullagh *et al*[11] reported the development of hyperthyroidism in a patient after section of the pituitary stalk and referred to a possible extra-pituitary substance as the cause of hyperthyroidism. Adams[12] produced evidence that such a substance is present in the blood of thyrotoxic patients and that it differs from normal thyroid stimulating hormone (TSH) by acting over a longer period of time. These authors have established that normal hypothalamic-pituitary-thyroid function has been superseded by an unidentified action, probably a result of a substance in plasma with TSH properties. This lays the foundation for the present postulate.

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Since stress is involved in hyperthyroidism, attention is directed to the division of the nervous system responsive to it, namely the sympathetic portion of the autonomic nervous system. Best and Taylor[13] describe the structure and function of this system, pointing out that the adrenal medulla, paraganglia and organ of Zuckerkandl are part of it and contain chromaffin tissue capable of secreting the catecholamines, epinphrine and norepinephrine. Normally, these are found in the blood in very small quantities, but larger amounts will increase oxygen consumption twenty to forty percent. Sympathin, a substance similar to but not identical with epinephrine is found in the peripheral endings of sympathetic nerve fibers. Greenberg and Gardner[14] refer to the finding of norepinephrine in brain tissue. Like many other hormones, catecholamines are synthesized with the aid of enzymes.

PROPOSED CONCEPT

It is proposed that an error in the stepwise synthesis of epinephrine from tyrosine could produce the substance with TSH-like action found by Adams.[12] This may occur in any one of the chromaffin structures as a local defect (or neoplasm) or in all of them as a general enzymatic block. The quantitative aspects will depend upon the amount of this substance released into the circulation. To illustrate, an individual with this defect who is not stressed will have negligible amounts, and therefore, he will be under normal hypothalamic control. If subjected to minor stress, his TSH-like substance will be only slightly increased and its action will be added to that of his normal TSH. Hypothalamic control will then reduce normal TSH so that the sum of the two will not exceed normal demand. Greater stress will increase the abnormal substance in varying amounts up to the level where it exceeds normal demand. At this point the patient will be hyperthyroid despite the fact that his normal TSH has been reduced to low levels.

The powerful nerve stimulating properties of thyroxin are well known. It is reasoned that the response of the sympathetic nervous system to stress is intensified by excessive thyroxin, and that after the original stress is withdrawn the thyroxin will act as the stressing agent. This will set up a vicious circle as follows: 1) Acute stress activates the sympathetic nervous system causing it to secrete the abnormal TSH-like substance. 2) This stimulates the production of more thyroxin. 3) The thyroxin stimulates the sympathetic nervous system to secrete more TSH-like substance, thus completing the circle. An effective interruption of the circle will allow the disturbed systems to tend towards normalcy. As the production of thyroxin is decreased by subtotal thyroidectomy, I^{131} therapy, thiourea drugs, iodine or sedation, there will be less stimulation of the sympathetic nervous system and less production of the abnormal TSH-like substance. The normal hypothalamic-pituitary-thyroid axis will again take over the regulation of thyroxin production and the patient will become euthyroid. It is equally clear that the patient will remain well only so long as the therapeutic measure prevents the re-establishment of the vicious circle. Regardless of the treatment used, if there be a sufficient amount of thyroid tissue to respond, enough TSH-like substance to stimulate that thyroid tissue and an adequate stress to trigger its production, all of the requirements for a relapse are present. This explains the high relapse rate experienced with all types of treatment.

At this point, a less likely but possible alternate concept should be mentioned. Epinephrine increases oxygen consumption in normal individuals and raises blood pressure more intensely in thyrotoxic patients than in normal persons. Because of these properties, it may be the offending substance in one whose thyroid innervation is hypersensitive to epinephrine. This would be contrary to Adam's observation.

Because of the implication of etiological significance, the following should be examined for any relation to the proposed concept. The rapid degredation of thyroxin seen in hyperthyroidism is discussed by Ingbar[15] who shows that it is present in active disease, in patients who have recovered and were euthyroid for two years and in their euthyroid relatives. The question is raised whether it is a reflection of the basic nature of the disease or the result of hypermetabolism per se. If it were caused by hypermetabolism, its presence in the euthyroid relatives would have to be explained on the basis of a previous unrecognized hyperthyroidism.

Dowling *et al*[16] have demonstrated that estrogen influences the thyroxin carrying capacity of plasma proteins which increases PBI without producing symptoms of hyperthyroidism. This does not seem to be related to the proposed action of TSH-like substance in a direct way, but it may reduce the amount of it indirectly in this way: Being more tightly bound to protein, thyroxin is less available to stimulate the sympathetic nervous system.

Exophthalmos has been shown by Dobyns and Wilson[17] to result from a substance which they have called exophthalmos producing substance (EPS). It is separate from normal TSH and was demonstrated in pituitary extracts and in the blood of thyrotoxic patients. Since the proposed concept excludes excessive pituitary secretions as the cause of hyperthyroidism, it must be assumed that the TSH-like substance has EPS action. The difference between patients relative to time of appearance and subsidence of exophthalmos is not readily explainable. It may be due to protein binding of the abnormal substance in the blood or to local factors in the orbit.

Because of the very small amounts present, Greer[15] states that it is unlikely that endogenous TSH in the plasma of euthyroid or hyperthyroid patients can be detected by assaying the blood. This probably applies to the abnormal substance as well.

CASE MATERIAL

Twenty cases of Hyperthyroidism were treated at Children's Hospital of Michigan during the past twenty years. A review of their case records was made and the data is presented in Table I. The totals are expressed as the number of cases out of twenty. The first ten were seen between 1941 and 1955, the other ten from 1955 to 1960. The threefold increase in the second period is attributed to the growth of the hospital census. However, some of it may be due to an increased incidence of hyperthyroidism in the childhood population and some to earlier diagnosis.

CLINICAL SYMPTOMS AND PHYSICAL FINDINGS

The Mayo series (1) consisting of 236 cases revealed a sex ratio of girls to boys of 6:1 for the entire group with 4:1 under ten years of age. Our figure was 1.5:1 for the entire group with no difference under ten years of age. Our race ratio of colored to white was 1.5:1 (the colored to white ratio for the hospital census is 3.7:1). The

TABLE I

Data Collected from the Records of 20 cases of Hyperthyroidism

GENERAL

Sex ratio	F:M	1.5:1
Race ratio	C:W	1.5:1
Age at onset	(2 to 5 yrs.	4
	(5 to 10 yrs.	9
	(10 to 15 yrs.	7
Height status	(Increased	14
	(Normal	2
	(Decreased	4
Weight status	(Increased	4
	(Normal	3
	(Decreased	13

SYMPTOMS		PHYSICAL FINDINGS	
Trigger mechanism	10/20*	Diffuse goiter	20/20
Nervousness	18/20	Nodular goiter	0/20
Irritability	15/20	Exophthalmos	18/20
Restlessness	13/20	Lid lag	9/20
Poor sleep	7/20	Increased bone age	2/11
Excessive appetite	11/20	Tremor	13/20
Weight loss	9/20	Tachycardia	19/20
Excessive sweating	9/20	Cardiac hypertrophy	6/18
Heat intolerance	7/20	Cardiac murmur	9/19
Vomiting	2/20	Thyroid bruit	5/20
Diarrhea	0/20	Increased BP and PP	18/20

LABORATORY

Increased BMR	11/11	Increased G T T	1/3
Decreased cholesterol	14/17	Abnormal urine	0/20
Increased PBI	13/13	Hgb. over 13 gm	5/20
Increased I^{131}	10/10	WBC over 10,000	5/20
Reversed A/G ratio	0/6	Increased Sed. rate	1/3

TREATMENT

Bed rest	17/20
Sedation	10/20
Iodine	5/20
Anti-thyroid drugs	16/20
Surgery	4/20

*The numerator indicates the total number of cases in which that category occured and the denominator shows the number investigated.

TABLE I

Data gathered from the Case Records of 20 cases of hyperthyroidism

| Case Number | Patient's Initials | Sex | Race | Date of Birth | Date of Admission | Age at onset in years | Height Percentile | Weight Percentile | Tremor mechanism | Nervousness | Irritability | Restlessness | Excessive appetite | Poor sleep | Weight loss | Excessive sweating | Heat intolerance | Diarrhea | Vomiting | Diffuse goiter | Nodular goiter | Exophthalmos | Bone age | Tremor | Extra ocular | Cardiac rate | Cardiac hypertrophy | Cardiac murmur | Thyroid bruit | Blood Pressure | B.M.R. | Cholesterol mg% | P.B.I. Mcg % | I131 (X normal) | A/G ratio | G T T | Urine (Albumin) | Hbg | WBC (M) | Polys (%) | Lymphs (%) | Monos (%) | Eos. (%) | Sed. rate (mm) | Bed rest | Sedation | Iodine therapy | Antithyroid drugs | RESULTS |
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age of onset was under five years in four cases; 13 were under ten years. The younger patients did not differ from the older ones with respect to severity, diagnosis or response to treatment.

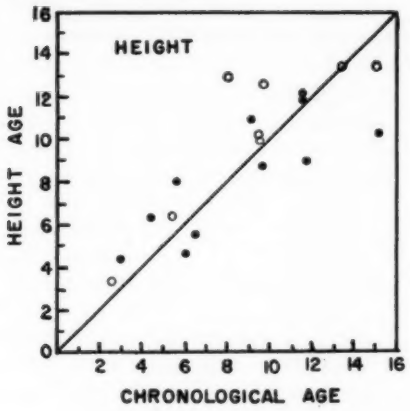

Figure 1

Scattergram of height ages of 20 cases of hyperthyroidism based on The Children's Medical Center, Boston — Anthropometric Chart. The dot sign indicates female. The open circle indicates male. The diagonal line is the normal for age. Numerals indicate age in years.

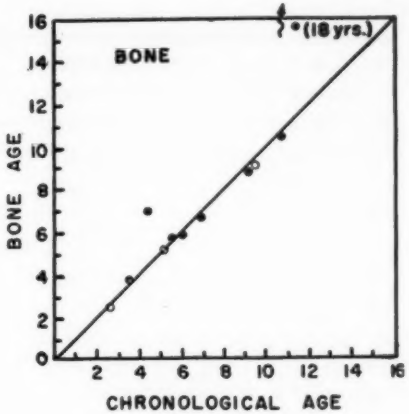

Figure 2

Scattergram of bone ages for 11 cases of hyperthyroidism in whom the estimations were made. The figures are from X-ray readings based on Todd's manual. The dot sign indicates female. The open circle indicates male. The diagonal line is the normal for age. Numerals indicate age in years.

Growth and development are effected by derangements of thyroid function. The well known dwarfism of cretins and lesser degrees of growth failure in mild hypothyroidism needs no comment. The accelerated growth seen in some cases of hyperthyroidism in children is not well understood. Talbot and Sobel[18] call attention to the fact that a deficiency in thyroid hormone will cause retardation of growth, but excessive amounts will not cause an increase. Data on height, weight and bone age are given in Table I. Figures 1 and 2, respectively, show height and bone age relations.

Age of onset is established on the basis of symptoms which the parents are able to remember. Of these, nervousness, diffuse goiter and exophthalmos are particularly significant and were selected for analysis. Table II gives the time of their appearance in relation to each other and to the stated time of onset.

Diffuse goiter was present in all cases at some time during the illness. In twelve it was present at onset; in the other eight it developed two to 21 months later. The size of the goiter varied from patient to patient, being larger in severe illness. This correlation does not obtain during treatment with thiourea drugs because size is increased by the action of the drug. The goiter may persist for some time after the patient has become euthyroid, but in most instances it recedes with improvement. The right lobe was larger than the left in 19 out of 20 children. Examination of the thyroid is difficult in children with thick short necks and in those who resist examination by flexing the head and throwing the shoulders forward. To overcome this, the patient is placed in front of the examiner in a sitting position with the head held

TABLE II

Time of Appearance of Exophthalmos, Goiter and Nervousness in Relation to the Onset and to each other.

Patient	Exophthalmos	Goiter	Nervousness
E. B.	1 month	1 month	X
D. B.	6 months	6 months	X
H. B.	4 months	4 months	X
R. R.	Absent	X	X
L. H.	12 months	X	X
D. W.	X	4 months	3/4 month
G. O.	X	21 months	12 months
L. S.	X	2 months	X
B. A.	X	9 months	X
S. W.	X	2 months	X
V. T.	X	X	1/2 month
M. H.	X	X	Absent
D. S.	X	X	Absent
R. T.	Absent	X	X
J. E.	X	X	X
D. W.	X	X	X
R. P.	X	X	X
G. P.	X	X	X
R. H.	X	X	X
L. C.	X	X	X

X—Appearance at onset. When the symptom appeared after onset, the time in months after onset is indicated in each instance.

in hyperextension. This will push the trachea forward, making the thyroid stand out prominently. Palpation can then be carried out without the reflex flexion.

Exophthalmos was present in 18 cases and was absent during the entire illness in two. It was present at onset in 14, being delayed one to 12 months after onset in four. Exophthalmometric measurements were recorded in two patients. Prior to the institution of this refinement, the evaluation was based on inspection. Kennedy[2] mentions that childhood exophthalmos may persist for years.

Nervousness was present in 18 out of 20 cases, being absent in two mild ones. The frequent occurrence of this symptom in conditions other than hyperthyroidism should be considered in differential diagnosis. Being the first to improve with treatment and the first to signal a relapse, nervousness becomes a valuable tool for following the progress of treatment.

A trigger mechanism was reported in only half of the cases and consisted of stress in the form of acute febrile illness, physical trauma or mental trauma prior

to the onset of the disease. Relapses and exacerbations are precipitated by stress. One girl in remission suffered a relapse following acute gangrenous appendicitis and another following an acute sore throat. Another in partial remission became worse after a sore throat.

Irritability, restlessness and tremor were present in the majority of cases. Excessive appetite was found in several, some of whom lost weight; a combination which has particular significance in hyperthyroidism. Excessive sweating and heat intolerance occurred in less than half of the cases. Gastro-intestinal symptoms were notably sparse. Cardiovascular findings were significant. Tachycardia was noted in 19 out of 20 cases and a wide pulse pressure in 18 out of 20.

LABORATORY PROCEDURES

The basal metabolic rate was used early in the series and was elevated in all but one case. Because it is difficult to perform in young children and is an indirect test of thyroid function, it is now used very little in the pediatric age group. Blood cholesterol was estimated in 17 cases and was below 170 mg. per 100 ml. in 10. Albumin globulin ratio and the glucose tolerance test were recorded in a few cases and revealed no significant pattern. Routine laboratory evaluations including complete blood counts and urine analyses showed the usual variations which one would expect in any series of 20 cases. There was no constant pattern that would fit into a conception of hypermetabolism. The sedimentation rate was not increased in the few cases in which it was done.

PBI was used diagnostically in 13 children. It was elevated above normal (4-7 mcg. per 100 ml.) in all cases, and in all but three it was above 10 mcg. per 100 ml., which we consider within the hyperthyroid range. It proved to be very helpful diagnostically and to follow the course of treatment. Ingbar and others[16] point out that PBI may change ahead of other criteria. I^{131} studies were done in ten cases, and all were reported as being in the hyperthyroid range.

TREATMENT

The choice of treatment is important in children; for as growing individuals they are thyroxin dependent. The therapeutic measure employed should produce a remission within a reasonable length of time and return the patient to a euthyroid state with an intact thyroidal system. If there were no other considerations, antithyroid drugs would be the treatment of choice in all cases as they come close to meeting these requirements. However, they need one to two or more years to effect a permanent remission and are slightly toxic to some individuals. If there is reason for haste such as a cardiac or other serious complication, or if the patient can not tolerate the drug, surgery would be the treatment of choice. Werner[15] stated that the concensus of opinion was that I^{131} therapy had no place in hyperthyroidism in children. The danger of producing total hyperthyroidism is too great and there is fear of possible carcinogenic effect.

The definitive treatment in this series was non-surgical with resort to surgery only if this failed. Propylthiouracil and methimazole (Tapazole) were the two anti-

TABLE III

Comparison of propylthiouracil and methimazole in the treatment of hyperthyroidism.

Patients	Dose/day in mg.	Duration of treatment.	Latest PBI.	
PROPYLTHIOURACIL				
R T	225	10 Days	——	Leucopenia. Transferred to methimazole.
G O	375	18 Mos.	17.6 μg.	Partial remission. Dose increased.
D S	150	3 Yrs.	4.5 μg.	Complete remission. Euthyroid now.
D B	225	——	——	No follow-up. Likely a remission.
D W	150	9 Mos.	6.4 μg.	Excellent for eyes. Partial remission.
S W	150	3 3/4 Yrs.	8.5 μg.	Complete remission. Euthyroid now.
L H	150	3 Mos.	15.5 μg.	Failure. Remission from surgery.
B A	150	6 Mos.	——	Remission B.M.R. -9% (1952).
R P	150	7 Mos.	——	Failure. Remission from surgery.
G P	75	11 Mos.	——	Partial remission. No follow-up.
METHIMAZOLE				
R T	30	3 1/2 Yrs.	7.5 μg.	Complete remission. Euthyroid now.
E B	30	?	——	No follow-up.
V T	15	2 2/3 Yrs.	6.6 μg.	Remission almost complete after relapse.
M H	5	1 Yr.	12.8 μg.	Partial remission. Dose too low.
L C	15	5 1/2 Yrs.	7.6 μg.	Complete remission. Irregular doseage.
L H	17.5	6 1/2 Mos.	——	Failure, epistaxis. Transferred to propylthiouracil.
R H	15	14 Mos.	——	Almost complete remission.
G P	15	2 Mos.	——	Rash. Transferred to propylthiouracil.

The daily dose was divided into three equal amounts given at eight hour intervals in all cases except M H who received her methimazole twice daily until recently.

thyroid drugs employed, and were found to be equally effective without variance in toxicity. Accordingly, a change was made from one to the other only if the one initially failed to produce a remission or gave an undesired reaction. Propylthiouracil was used in ten cases. Two were later transferred to methimazole, one because of leucopenia after ten days of treatment and the other because of failure to achieve a remission within three months plus a severe epistaxis. Eight were considered successful. Methimazole was used in eight cases, six of which were successful. One developed a rash after two months treatment and was transferred to propylthiouracil; the other failed to improve after six and one half months and was treated surgically. Table III gives the details of the fifteen cases in which these two drugs were used. Van Wyk and his group[3] report considerable success from the use of dessicated thyroid to reduce the size of the goiter during treatment with anti-thyroid drugs. We did not use it for this purpose because it seemed illogical. The rationale of thyroid feeding to reduce goiter is based on the premise that goiter is produced by excessive amounts of TSH and that exogenous thyroxin will surppress TSH production. In hyperthyroidism, there is already an excess of thyroxin in the blood which will have reduced TSH to its

fullest extent. The giving of more thyroxin in the form of thyroid feeding would appear to be superfluous. Also, Werner[9] has shown that pituitary TSH is not primarily involved in hyperthyroidism; therefore, little will be gained by reducing it. The exception to this is that the PBI may be reduced to hypothyroid levels by anti-thyroid therapy, and this will call for more TSH. Admittedly, exogenous thyroid would be of value here, but it would be more logical to allow the PBI to rise to euthyroid levels homeostatically by reducing the amount of anti-thyroid drug. The same considerations will apply to exophthalmos.

Five cases were treated initially with other agents. Two were treated surgically before antithyroid drugs were available. One received thiouracil and was reported to have recovered. Two very mild cases are presently being treated with sedation alone.

Treatment was considered successful if the following were achieved: 1) Prevention of serious organ failure or complication. 2) Control of nervousness within two or three weeks. 3) A continuation of normal growth and development. 4) Ability to attend school during treatment. 5) A remission in one to two years. 6) A gradual subsidence of goiter and exophthalmos following remission. On the other hand, if successful treatment is interpreted to mean permanent cure, then all presently employed measures are inadequate. In a sense, they represent symptomatic treatment in that they treat only certain parameters of the disease without eliminating the cause.

Four children were treated surgically by subtotal thyroidectomy. All of them experienced a satisfactory remission and none has reported a relapse within the period of effective follow-up (four years in three patients and seven years in the other). One patient developed a mild hypothyroidism, but there were no other post-operative complications such as thyroid storm, hypoparathyroidism or paralysis of the recurrent laryngeal nerve.

COMMENT

Ideas on the etiology of hyperthyroidism change from time to time. Plummer's view of an iodine poor hormone with toxic properties was challenged by Marine who proposed an extra-thyroidal mechanism involving the pituitary gland or sympatho-adrenal system. An acceleration of the hypothalamic-pituitary-thyroid function came into favor, but this was rendered untenable by the extra-pituitary intrathyroidal concept. Evidence then appeared which placed the cause outside the thyroid in the form of an abnormal TSH-like substance. The present postulate proposes that this substance is produced by chromaffin tissue, getting back to Marine's sympatho-adrenal suggestion.

In attempting to correlate the thinking on etiology with data obtained from the case records, the following conclusion was reached — there is a flexibility in all aspects of the disease which is exemplified by the difference between patients relative to symptoms, physical findings, laboratory work and results of treatment. Several possibilities were considered in an effort to explain these variations: 1) Is there a qualitative variation in the etiological factor? This is unlikely whether it be epinephrine or a chemical variant caused by an enzymatic block. It is more apt to be quantitative depending upon the amount elaborated. 2) Do changes in the stability of the nervous

system effect patient response sufficiently to cause variations? This would seem to be the logical explanation for quantitative aspects because nervous irritability governs both reception of stress stimuli and the production of catecholamines by the sympathetic nervous system. 3) Do temporal relations of the pathological processes account for differences? The data show that the development of individual symptoms and physical findings have different time schedules compared to each other and to time of onset. Early symptoms such as nervousness, tachycardia and hypermetabolism are likely the result of direct thyroxin action upon the cells; whereas the later manifestations like goiter, exophthalmos, cardiac hypertrophy and accelerated degredation of thyroxin are the consequences of this abnormal action. As such, more time is required to produce them, and being more deeply entrenched, their subsidence is slower during remission. 4) Does a pluri-casual pathogenesis fit into hyperthyroidism? Selye* has shown that cardiac infarction will result from stress only if the test animal were previously treated with cortisone. Applying this line of reasoning to hyperthyroidism, the etiological factor may have the additional action of a conditioner or catalyst without which thyroxin is unable to produce its characteristic pathological results. 5) Is hyperthyroidism a symptom complex rather than a separate disease entity? The plausibility for this approach gets support from the number of different etiologies which have been proposed over the years, all of which may be valid. In short, toxic goiter may be a grouping of reactions involving the thyroid but not dependent upon any single causative factor.

A careful consideration of these possibilities favors the acceptance of the proposed postulate of a single etiology for a distinct disease entity in which the observed differences represent variations in response.

SUMMARY

A new concept of etiology for hyperthyroidism is described which proposes that an abnormal thyroid stimulating substance is elaborated by chromaffin tissue of the adrenal medulla and other portions of the sympathetic nervous system in response to stress. Data collected from 20 cases of hyperthyroidism in children were analyzed with special attention to the flexibility of the findings and response to treatment. This was correlated with the concept.

REFERENCES

1. Kennedy, R. L. J., and Hayles, A. B.: The thyroid gland, In, McQuarrie, I., and Kelley, V. C., Eds.: Brennemann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Co. 1957, v. 1 Chap. 38, pp. 1-43.

2. Hayles, A. B., Kennedy, R. L., Beahrs, O. H., and Wollner, L. B.: Exophthalmic goiter in children, J. Clin. Endocr. Metab. 19:138, 1959.

3. Van Wyk, J. J., Grumbach, M. M., Shepard, T. H., II, and Wilkins, L.: The treatment of hyperthyroidism in childhood with thiouracil drugs, Pediatrics 17:221, 1956.

4. Arnold, M. B., Talbot, N. B., and Cope, O.: Concerning the choice of therapy for childhood hyperthyroidism, Pediatrics 21:47, 1958.

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*Selye, H.: The Pluricausal Cardiopathies, 40th Annual Beaumont Lecture of the Wayne County Medical Society, Detroit, 1961 (April 3).

5. Li, M. C., Rall, J. E., MacLean, J. P., Lipsett, M. B., Ray, B. S., and Pearson, O. H.: Thyroid function following hypophysectomy in man, J. Clin. Endocr. Metab. 15:1228, 1955.

6. Moschcowitz, E.: Nature of Graves' disease, Arch. Int. Med. 46:610, 1930.

7. Thompson, W. O.: Changing concepts in thyroid physiology and therapy, J. Clin. Endocr. Metab. 13:457, 1953.

8. Canary, J. J., Schaaf, M., Duffy, B. J., Jr., and Kyle, L. H.: Effects of oral and intramuscular administration of reserpine in thyrotoxicosis, New England J. M. 257:435, 1957.

9. Werner, S. C., Spooner, M., and Hamilton, H.: Further evidence that hyperthyroidism (Grave's disease) is not hyperpituitarism: effects of triiodothyronine and sodium iodide, J. Clin. Endocr. Metab. 15:715, 1955.

10. Becker, D. V.: Effects of hypophysectomy on certain parameters of thyroid function in two patients with Graves' disease, J. Clin. Endocr. Metab. 19:840, 1959.

11. McCullagh, E. P., Reynolds, C. W., and McKenzie, J. M.: Hyperthyroidism after section of the pituitary stalk for malignant exophthalmos: report of a case, J. Clin. Endocr. Metab. 20:1029. 1960.

12. Adams, D. D.: The presence of an abnormal thyroid-stimulating hormone in the serum of some thyrotoxic, J. Clin. Endocr. Metab. 18:699, 1958.

13. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 5, Baltimore, Williams & Wilkins Co., 1950.

14. Greenberg, R. E., and Gardner, L. I.: The excretion of free catecholamines by newborn infants, J. Clin. Endocr. Metab. 20:1207, 1960.

15. Ingbar, S., Greer, M. A., and Werner, S. C.: [Thyroid and iodine metabolism] In, Discussion of: Duration of Graves' disease after sustained remission of symptoms, Pediat. Res. Conf. (Ross Laboratories, Columbus, Ohio) Report No. 20:45, 1957.

16. Dowling, J. T., Freinkel, N., and Ingbar, S. H.: The effect of estrogens upon the peripheral metabolism of thyroxine, J. Clin. Invest. 39:1119, 1960.

17. Dobyns, B. M., and Wilson, L. A.: An exophthalmos-producing substance in the serum of patients suffering from progressive exophthalmos, J. Clin. Endocr. Metab. 14:1393, 1954.

18. Talbot, N. B., and Sobel, E. H.: Endocrine and other factors determining the growth of children, Advances Pediat. 2:238, 1947.

DERMATITIS HERPETIFORMIS ASSOCIATED WITH A FOCUS INFECTION

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Dermatitis Herpetiformis[1,2,3,4] is a chronic disease of the skin characterized by lesions of various morphs including erythematous, papular, vesicular, bullous, and pustular lesions. The vesicular form of the disease usually predominates but polymorphism is common. In some cases the primary lesions are not seen and only crusted papules, excoriations, hyperpigmentation, depigmentation, and atrophy are evident. Severe pruritus is an important feature of dermatitis herpetiformis and often the itching is accompanied by a burning sensation. Usually the lesions occur in symmetrical groups and predominate on the elbows, knees, sacral region, trochanteric, and scapular regions.

At various times reports[5,6,7,8,9,10] referrable to the role of foci of infection in dermatitis herpetiformis have appeared in the literature.

We have observed a patient, in whom the administration of broad spectrum antibiotics and the removal of a source of infection, has appeared to influence the course of the disease.

CASE REPORT

A 49-year-old, white female was first seen on August 29, 1959 because of an acute pruritic eruption of two months' duration, which involved the trunk and extremities. It consisted of grouped vesicles and bullae surmounted on a diffuse, mottled, erythematous, and hyperpigmented background. The rest of the physical examination was non-revealing.

Because of the severity of her eruption, she was admitted to the hospital on September 3, 1959.

Her laboratory studies in the hospital were as follows: white blood count was 8,500 per cu. mm. with 82% segmented forms, 9% lymphocytes; 4% monocytes, and 5% eosinophils. The hemoglobin was 13 gm.%; two hour P.C. blood sugar 90 mg.%; serum urea nitrogen 16 mg.%, and serologic test for syphilis was non reactive. Microscopic examination of the urine revealed per high powered field, 20-40 epithelial cells, 20 white cells, bacteria and trichomonas. Urine obtained for culture grew on one occasion B. Proteus very sensitive to chloromycetin, moderately sensitive to streptomycin, and resistant to tetracycline. Stools were negative for ova and parasites. The chest x-ray, upper and lower GI series, cholecystogram, and proctoscopy were non revealing. Skin tests to hemolytic strep, strep. viridans, and staph. toxoid were negative. Dental x-ray revealed severe periodontitis.

A biopsy was taken of a vesicular lesion. The vesicle was subepidermal and contained a moderate exudate of inflammatory cells, many of which were eosinophils.

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There was no significant change in the epidermis which was, however, slightly thinned over the vesicle. There was an exudate of inflammatory cells, mostly mononuclears, about the adnexal structures and vessels of the corium. The histologic findings were compatible with a diagnosis of dermatitis herpetiformis.

Sulfapyridine, prednisone, and nicotinic acid were given in adequate doses and did not influence the course of the disease. Seven days after admission, tetracycline 250 mgm. q.i.d. was started. Two days later the pruritus has disappeared and only an occasional new vesicle was noted. This was in striking contrast to almost complete lack of response to previous therapy. For the next nine days tetracycline was continued in the same dosage and the patient remained relatively free of signs or symptoms of the disease. The tetracycline was then discontinued and after 24 to 48 hours new pruritic vesicles appeared.

On consultation with the oral surgery department, it was decided that a full mouth dental extraction should be done. This was advised because of severe periodontitis. Just prior to the extraction of her teeth, tetracycline was re-instituted for the second time and continued five days. With the administration of tetracycline and the dental extractions her skin cleared. It is interesting to note that during a follow up period of twenty one months, the patient has had no recurrence of her skin lesions.

DISCUSSION

The relationship of dermatitis herpetiformis to a focus of infection has been reported at various times in the past. However, the standard dermatologic text books make little mention of this fact. Sutton,[1] in his discussion on therapy of this eruption mentions that focal infection should be eliminated. Ormsby and Montgomery[2] state dermatitis herpetiformis has followed infections, but say nothing about eliminating infection in their section on therapy. In Pillsbury, Shelly, and Kligman's[3] text book, the only reference to infection is "antibiotic agents have little or no effect upon dermatitis herpetiformis, unless there is active secondary bacterial infection." Andrews[4] does mention in his section on therapy "focal infection, if present, should be treated as some cases have thus been permanently cured."

Irving[5] presented a patient with dermatitis herpetiformis in 1918 to the Minnesota Dermatologic Society. After an infected tonsil was removed, his lesions improved significantly. Later Epstein[6,7] reported on two patients with localized bullous eruptions on the skin and one with a generalized bullous eruption, which cleared after infected teeth were removed.

Callaway and Sternberg[8] treated a patient who had dermatitis herpetiformis and bronchiectasis. They prepared an autogenous vaccine of pneumococcus type VII, isolated from the patient's upper respiratory tract. Apparently administration of the vaccine over a period of time resulted in involution of the lesions. Intradermal tests with the vaccine caused a bullous reaction at the test site and it was their opinion that bacterial allergy was important etiologically in this patient.

Intradermal injections of various bacterial vaccines were given by Swartz and Lever[9] to twelve patients with dermatitis herpetiformis and in twenty patients with

other skin diseases. In five of the patients with dermatitis herpetiformis, local vesicular reactions occurred with Bact. Coli vaccine. In one of the five patients a vesicular reaction followed staph vaccine at the test site and another strep vaccine. They felt that this response was based on bacterial allergy.

Epstein[10] was able to produce bullous delayed reactions to skin tests with streptococci antigens in two children with dermatitis herpetiformis. He also mentioned in his paper that Bernhardt and Leone had produced similar type reactions with other vaccines. He felt that bacterial allergy may be important etiologically in a large significant percentage of patients with dermatitis herpetiformis.

At various times during the past seventeen years, a number of investigators have reported on the use of both penicillin and broad spectrum antibiotics in the management of dermatitis herpetiformis.

Thus Carpenter and Hall[11] gave penicillin to six patients with dermatitis herpetiformis and controlled their eruptions. Their thought was that bacterial allergy might be important in these patients. Both Saffron[12] and Grund[13] found aureomycin effective in a small series of patients. Robinson and Robinson[14] also reported good results with aureomycin in six out of ten patients with dermatitis herpetiformis. In a recent paper Cornbleet[15] mentioned that antibiotics are helpful in dermatitis herpetiformis. Unfortunately no mention was made in these papers about a possible source of infection.

It would appear from our case and also from the literature, that some patients with dermatitis herpetiformis have a bacterial allergy which may contribute partially or wholly to their disease. Thus it behooves all of us to investigate patients with dermatitis herpetiformis for foci of infection. Even though removing a focus of infection may not cause a permanent remission, it may permit a patient to live for a relatively long period of time without any manifestations of his disease.

SUMMARY AND CONCLUSIONS

A patient with dermatitis herpetiformis, who improved while taking broad spectrum antibiotics, and had a prolonged remission when a focus of infection was removed, is reported. It is important when treating a patient with dermatitis herpetiformis to search for a course of infection and if possible remove it. If there is a focus of infection, broad spectrum antibiotics may give the patient spectacular relief prior to the definitive treatment of it.

REFERENCES

1. Sutton, R. L., Jr.: Diseases of the Skin, ed. 11, St. Louis, C. V. Mosby, 1956, pp. 976-981.

2. Ormsby, O. L., and Montgomery, H.: Diseases of the Skin, ed. 8, Philadelphia, Lea & Febiger, 1954, pp. 419-425.

3. Pillsbury, D. M., Shelley, W. B., and Kligman, A. M.: Dermatology, Philadelphia, W. B. Saunders Co., 1956, pp. 793-797.

4. Andrews, G. C.: Diseases of the Skin, for Practitioners and Students, ed. 4, Philadelphia, W. B. Saunders Co., 1954.

5. Irvine, H. G.: Dermatitis herpetiformis (case report), J. Cut. Dis. 36:64, 1918.

6. Epstein, S.: Persistent localized bullous eruption associated with focal infection, Arch. Dermat. & Syph. 56:452, 1947.

7. Epstein, S., and Macauley, W. L.: Bullous eruption resembling dermatitis herpetiformis, associated with focal infection, Arch. Dermat. & Syph. 57:736, 1948.

8. Callaway, J. L., and Sternberg, T. H.: Bacterial allergy: etiologic factor in dermatitis herpetiformis, Arch. Dermat. & Syph. 43:956, 1941.

9. Swartz, J. H., and Lever, W. F.: Dermatitis herpetiformis; immunologic and therapeutic considerations, Arch. Dermat. & Syph. 47:680, 1943.

10. Epstein, S.: Bullous reactions to bacterial antigens in dermatitis herpetiformis, J. Invest. Derm. 33:31, 1959.

11. Carpenter, C. C., and Hall, W. H., Jr.: Treatment of dermatitis herpetiformis with penicillin, Arch. Dermat. & Syph. 51:241. 1945.

12. Saffron, M. H.: Dermatitis herpetiformis; report of 2 cases in children treated with aureomycin, J. M. Soc. New Jersey 46:440, 1949.

13. Grund, J. L.: Oral administration of aureomycin in treatment of certain dermatoses, New England J. Med. 242:928, 1950.

14. Robinson, H. B., and Robinson, H. M., Jr.: Aureomycin, oral, intravenous and by local application in treatment of dermatoses, South. M. J. 44:1116, 1951.

15. Cornbleet, T.: Long-term therapy of acne with tetracycline, A.M.A. Arch. Derm. 83:414, 1961.

CLINICAL EVALUATION OF METHYCLOTHIAZIDE, A NEW POTENT LONG-ACTING ORAL DIURETIC DRUG

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The advent of thiazide diuretic drugs has opened a new and effective means of helping the patient with edema. Many potent oral agents have been developed which cause a diuresis of salt and water. The parent compound is chlorthiazide, the pharmacology of which has been described by Ford, Moyer and Spurr.[1] The drug stimulates sodium and chloride excretion and, to a lesser extent, potassium and bicarbonate excretion. It works both orally and intravenously, but is excreted very rapidly when given I.V.[2] The urinary excretion patterns are similar to the mercurial drugs, except for greater potassium excretion. The optimum dose of chlorthiazide is 500 mg. b.i.d.

Although the organomercurials are the most potent or effective diuretics when maximum or immediate diuresis is required, they must be given parenterally and therefore have this disadvantage. Thiazide drugs are effective when given daily and thus also have an advantage over the oral carbonic anhydrase inhibitors such as acetazolamide, which must be given at several days intervals. The latter diuretics lead to a great deal of base bicarbonate excretion and the ensuing acidosis makes them temporarily ineffective. In addition, carbonic anhydrase inhibitors have only moderate naturetic activity. Toxicity or tolerance after long term therapy is rarely a problem with the thiazides. Peak effect from chlorthiazide is at four hours and duration of action is from six to eight hours.

A number of derivatives of chlorthiazide have become available in recent years,[2,4] since Novello and Sprague's first report.[3] Changes in positions 3, 4 and 6 appear to be most significant. Hydrochlorthiazide has 10 times the milligram potency of chlorthiazide, but exactly the same naturetic and kaluretic excretion pattern at the peak dose. Quantity of chloride excreted, however, is greater. Flumethiazide has a CF_3 instead of Cl at position 6 and is similar to chlorthiazide except that potassium excretion levels off at a lower dose range. Hydroflumethiazide is similar to hydrochlorthiazide, but has a smaller kaluretic effect. Benzhydroflumethiazide and trichlormethiazide differ from hydroflumethiazide and hydrochlorthiazide only in their effective dose range, which has been reduced to 1-2 mg. It should be emphasized that the effective sodium excretion with all the thiazides so far available is practically identical, despite the wide variation in optimum doses.[5]

Recently, our group had the opportunity to study a new thiazide derivative. The drug, methyclothiazide,† is the first of these agents to have a CH_3 substitution.

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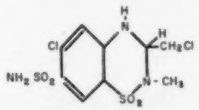
†Supplied as Enduron by Abbott Laboratories, North Chicago, Illinois.

Methyclothiazide

Methyclothiazide is a benzothiadiazine (6 chloro-3-chloromethyl-2-methyl-7-sulphamyl-3,4-dihydro-1,2,4,-benzothiadiazine). Its basic pharmacology is similar to that

Formula



METHYCLOTHIAZIDE

of hydrochlorothiazide.[5,6] Standard Fuchs Bioassay techniques were used in the evaluation. Since our work the drug has been marketed under the trade-name of Enduron.

Studies were carried out on both hospitalized ("dry") patients and on an outpatient basis with edematous individuals. These were done as follows:

A. INPATIENT BIOASSAY STUDIES:

1. **Electrolyte Excretion and Dose Response Curve:** A group of hospitalized non-edematous patients were studied to determine the effects of varying doses of the drug on urinary electrolyte excretion. All had normal cardiorenal function and most were orthopedic patients. Each patient was placed on a metabolic diet containing 50 mEq. sodium (one gram NaCl) and from 2000 to 3000 cc. of water daily. Twenty-four hour urine specimens were collected and analyzed for total milliequivalents of sodium, potassium and chloride. Total creatinine excretions were also determined. After a control period of four to seven days during which the patient was equilibrated (sodium excretion was stabilized at approximately 90% of dietary intake) the drug was given as a single morning dose. The twenty-four hour urinary electrolyte excretion in milliequivalents was measured on the day following the drug administration. The difference between these values and the control figures is considered to be a measure of the naturetic effect of the drug. A dose response curve was obtained by studying patients in the above manner. The doses were as follows: 2.5 mg. single dose; 5 mg.; 7.5 mg.; 10 mg.; 12.5 mg.; 15 mg.; and 10 mg. (b.i.d.). Between four and ten patients were studied at each of these dose levels.

2. **Duration of Response to a Single Oral Dose:** Several other patients were studied in order to determine the duration of response to a single oral dose of the drug. After obtaining control values of urinary electrolyte excretion while on a 50 mEq. sodium diet, a single 10 mg. dose of methyclothiazide was given. The urine collections were made at two hour intervals for 24 hours and the increase in sodium, chloride and potassium excretion during each two hour period was determined. Actually, only 11 collections were made in a 24 hour period because one sample went from 2:00 A.M. to 6:00 A.M.

3. **Renal Function Studies:** One hospitalized patient without any overt evidence of kidney disease was studied in order to determine the effects of a single

dose of methyclothiazide on glomerular filtration rate, renal plasma flow, urine volume and urinary electrolyte excretion. The blood pressure and serum sodium and potassium levels were noted. Following three 20 minute control urines, the patient received 10 mg. of methyclothiazide orally. Serial determinations of urine and blood values were done at intervals for approximately six hours following the drug administration.

B. OUTPATIENT STUDIES:

1. **Weight Response Curve After Varying Doses:** An acute 48 hour response by weight loss was determined in 25 patients in the Diuretic Clinic at Hahnemann Medical College and Hospital. These patients had all shown evidence of mild to moderate congestive heart failure and were on maintenance doses of digitalis. All of these patients had previously required at least one or two injections of a mercurial diuretic per week in order to maintain them in an edema free state. The etiology of their cardiac failure was varied. In most cases the cause was arteriosclerotic heart disease, others had chronic rheumatic valvular diseases. The age range was 22 to 68 years.

Prior to this phase of the study the patients were given no diuretic therapy for at least a week to 10 days. The remainder of the medication was unchanged. Each patient was weighed in the morning before breakfast and after voiding. Methyclothiazide was then given for two days and the weight again recorded. All patients were studied in this manner at doses of 2.5 mg. daily, 5 mg. daily, 10 mg. and 20 mg. daily. At least five to ten days without diuretics were allowed between doses, during which time edema fluid reaccumulated.

2. **Chronic Administration of Drug:** The response of this same group of patients to the chronic administration of the drug was also studied. Following a five to ten day period without diuretic agents each patient was placed on methyclothiazide so that he received his medication daily for a five week period. Serum electrolytes including sodium, potassium, chloride, CO_2 combining capacity, blood urea nitrogen and a complete blood count were determined before and upon completion of the chronic study. In addition, serum uric acid was also determined. These blood tests were also performed at two weeks to note any early or transient changes. Each patient was weighed and examined every week during the chronic study and was observed for signs of toxicity, side effects and any change in the blood pressure.

RESULTS

Bioassay Studies: The responses to several different doses of methyclothiazide are shown in Table I and graphically in Fig. 1. The doses ranged from 2.5 mg. daily to 10 mg. b.i.d. Although there is an increase in naturetic activity observed as the dose is raised from 2.5 mg. daily to 10 mg. daily, at which level maximum naturetic effect was observed, it should be noted that maximal kaluretic activity occurred at a 5 mg. daily dose level. Following this, there was a plateauing of potassium excretion at higher doses. Increasing the dose above this resulted in a significant, almost doubled, naturetic activity without any rise in kaluretic activity being observed. At

TABLE I

DOSE RESPONSE TO METHYCLOTHIAZIDE BY ELECTROLYTE EXCRETION

DOSE	2.5 mg. O.D.			5 mg. O.D.			7.5 mg. O.D.			10 mg. O.D.			12.5 mg. O.D.			15 mg. O.D.			10 mg. B.I.D.		
No. of Pts.	10			6			4			10			4			4			4		
Urinary Electrolyte	Na	Cl	K	Na	Cl	K	Na	Cl	K	Na	Cl	K	Na	Cl	K	Na	Cl	K	Na	Cl	K
Increase in milliequivalents above control per 24 hour urine collection	10	22	12	23	45	1	53	80	16	81	116	52	86	117	46	61	60	9	63	70	26
	15	23	16	37	55	31	55	107	10	101	98	19	94	95	11	68	70	16	14	129	12
	22	62	21	36	79	39	129	166	28	103	120	17	100	119	37	171	198	59	129	129	7
	23	22	4	78	97	29	141	187	72	112	111	17	208	203	40	180	177	27	130	173	10
	24	39	-7	99	93	19				113	73	19									
	45	32	-2	142	222	82				120	141	14									
	48	53	10							129	159	53									
	57	77	28							157	202	26									
	66	49	5							164	149	62									
	87	92	15							170	179	29									
Average increase for patients studied	40	45	10	69	99	32	95	135	32	125	135	31	122	134	34	120	126	27	108	125	14

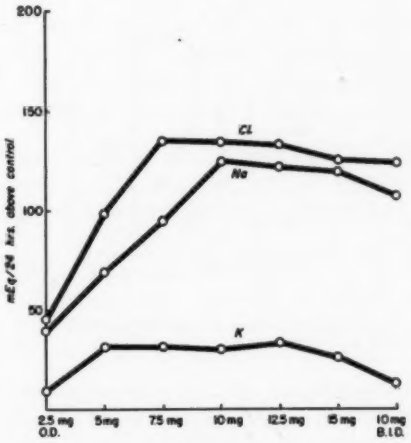


Figure 1

Dose response curve; urine electrolyte patterns.

an optimal dose level of 10 mg. daily, ten patients were studied and the average increase above the control level in milliequivalents of sodium per 24 hour urine, was found to be 125 mEq. The increase in kaluresis was but 31 mEq. per 24 hour urine collection. One patient who received several separate doses over a period of two weeks developed acute pain, tenderness, swelling and inflammation of the right knee; at this time her uric acid level was 7.3 mg.%.

The duration of response to a single 10 mg. oral dose of methyclothiazide is shown in Fig. 2, 3 and 4. These charts show the total 24 hour urine electrolyte excretion and urine volume per two hour collection period for sodium, potassium and chloride respectively. These values are total values and not increases above control levels. The urine volume per collection period can be noted on the charts. It can

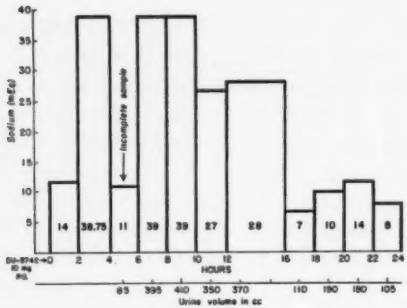


Figure 2

Total sodium excretion in milliequivalents over 24 hour period.

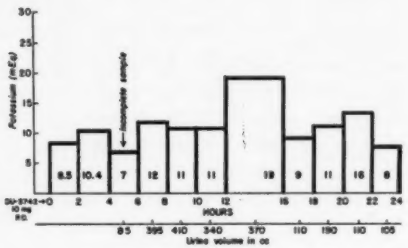


Figure 3

Total potassium excretion in milliequivalents over 24 hour period.

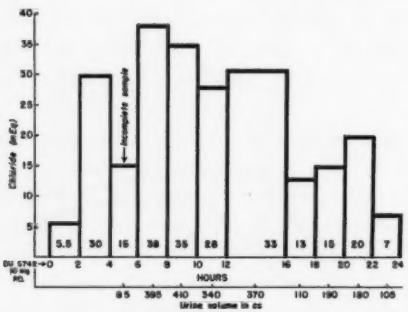


Figure 4

Total chloride excretion in milliequivalents over 24 hour period.

readily be observed that the onset of naturesis occured two hours after the oral dose and that significant levels of naturesis persisted for 14 hours, until 16 hours after the oral dose. Significant chloruresis persisted somewhat longer until the 22nd hour. The maximum urine volume per two hour period occurred between the eighth and tenth hour. These results show that methyclothiazide is absorbed rapidly through the gastrointestinal tract and that its effects can be seen within two hours after administration. This study was done in one patient and it should be observed that the urine collection between the fourth and sixth hours was incomplete. Ford has noted naturesis and chloruresis above the control for periods longer than 24 hours.[7]

Renal function studies were obtained in one patient. The results are shown in Table II. The patient received 10 mg. of methyclothiazide orally. An increase in

glomerular filtration rate as determined by endogenous creatinine clearance was observed. Peak chloruresis occurred between five and six hours after administration

TABLE II

RENAL FUNCTION STUDIES IN NON-EDEMATOUS YOUNG MALE AFTER 10 MG. METHYCLOTHIAZIDE GIVEN ORALLY

B.P.	110/72	110/60	108/66	106/68	110/72	112/70	114/72	116/70	124/70	122/78	124/70	122/70	124/70
Urine Vol. (cc.)	88	93	116	96	124	96	84	86	164	162	196	92	84
GFR cc/min.	72	72	80	87	117	105	88	105	141	121	127	112	115
uEq. Per Minute K	50	60	89	83	98	69	52	53	98	98	81	99	89
Cl.	6	12	13	10	30	35	40	70	165	300	349	309	274
Na.	71	60	53	60	69	78	97	141	321	375	365	368	309
Time Hours	0	½	1½	2	2½	3	3½	4	4½	5	5½	6	6½

of the drug. The kaluretic response paralleled the naturetic response in onset and duration but not in magnitude. These studies show that oral methyclothiazide causes a significant increase in naturesis and chloruresis, the onset of which is prompt and which lasts for at least six and one-half hours. No marked kaluretic activity was observed, nor were there any significant changes in the blood pressure. Sodium excretion well in excess of 300 microequivalents per minute started about four-and-a-half hours and continued until the end of the experiment.

Outpatient Studies: The acute 48 hour response by weight loss is shown in Fig. 5. Twenty four patients on 2.5 mg. daily for two days lost an average of 0.51 pounds. Twenty one patients on 5 mg. lost an average of 1.12 pounds. Twenty five

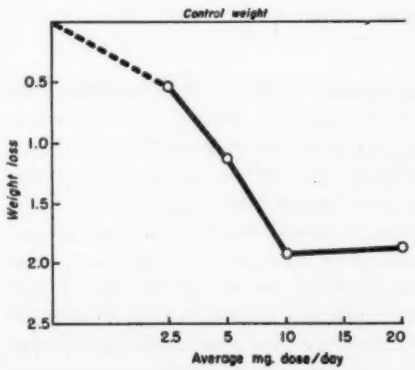


Figure 5

Average weight loss in congestive heart failure patients after 48 hours of therapy.

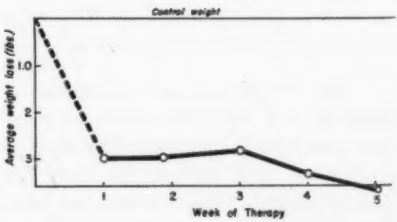


Figure 6

Average weight loss in congestive heart failure patients during chronic therapy (10 mg/day).

TABLE III

WEIGHT CHANGES AFTER CHRONIC ADMINISTRATION OF METHYCLOTHIAZIDE (10 mg. daily for 5 weeks)

PATIENT	CONTROL	2 WEEKS	5 WEEKS
1	124 lbs.	118 lbs.	119 lbs.
2	138	128	129
3	114	112	115
4	127	126	125
5	160	155	156
6	177	175	174
7	182	180	180
8	187	185	182
9	179	178	180
10	127	125	121
11	113		112
12	209	208	209
13	163	164	165
14	140	136	131
15	179	176	176
16	148	145	138
17	143	135	133
18	167	167	167
19	143	141	138
20	144	142	139
21	264	263	259
22	148	141	

patients on 10 mg. lost an average of 1.91 pounds and twenty three patients on 20 mg. lost an average of 1.88 pounds. The "p" values for the 10 mg. dose and the 20 mg. dose are less than 0.001 and it can be seen that the 10 mg. daily dose for two days caused a significant weight loss. There were no undesirable side effects from the drug such as nausea, vomiting or signs of specific sensitivity. At 20 mg. daily there was no greater weight loss; this would coincide with the somewhat decreased naturetic effect at doses higher than 10 mg. daily. These results will be seen in the dose response curves (Fig. 1).

The weight response to chronic administration of 10 mg. of methyclothiazide daily for five weeks is shown in Table III and graphically in Fig. 6. These results were obtained in an outpatient study of patients from the Diuretic Clinic. Twenty six patients who received the drug for one week lost an average of 2.97 pounds during the first week. Twenty one patients who received the drug for two weeks lost an average of 3.00 pounds for the two week period. Nineteen patients received the drug daily for three weeks and lost an average of 2.44 pounds during the period. Twenty one patients received the drug for four weeks and lost an average of 3.29 pounds over the total four week period and 21 patients received the drug daily for five weeks and lost an average of 3.74 pounds for the five week period. The response of these patients to a 10 mg. daily dose of methyclothiazide was, as a whole, satisfactory in that they were maintained in an edema free state without significant side effects or changes in blood pressure. There were a few patients who did gain

weight with the long term administration of the drug. All but a very few patients lost a large percentage of their total weight loss during the first week or two of therapy. Most of the patients maintained this weight loss although a few did show a weight gain between the second and fifth week.

Table IV shows the **serum electrolytes (sodium, potassium, chloride and CO_2) and complete blood count in all patients in the chronic study** before and upon completion of the study. It should be noted that there was a consistent decrease in the serum sodium although this at no time fell below 130 mEq/1. There was also a consistent decrease in serum chloride. There was no significant change in the serum potassium or CO_2 levels nor was there any significant hyperuricemia noted during this five week period. However, a single patient, who did not show acute gouty arthritis, did have a serum uric acid elevation from 4.9 mg.% to 6.9 mg.%. It is interesting to note that in several of the patients a slight leukocytosis was observed, although the significance of this is unexplained. Emil Conason, working with a population of hypertensive patients, has made a similar observation.[9] He feels that the WBC increase, which may occur in as many as 50% of patients on this drug, is an "epiphenomenon" or specific side effect. Four patients had BUN elevations up to 30 mg.% and another went from a control of 29 mg.% to 37 mg.%.

SUMMARY AND CONCLUSIONS

In order to evaluate a new diuretic agent, methyclothiazide, a clinical investigation was performed which included the following studies:

A. **Inpatient Bioassay Studies:**
   1. Urinary electrolyte excretion patterns before and after a single oral dose, in "dry" patients on a measured sodium intake.
   2. Dose response curves as determined by urinary sodium excretion in patients who received varying oral doses.
   3. Duration of response after a single oral dose.
   4. Renal function studies were performed on one patient. They included the effect of methyclothiazide on glomerular filtration rate, fractional urine volumes and electrolyte patterns.

B. **Outpatient Clinic Studies:**
   1. Weight response curves as determined by weight changes after administering varying doses of the drug for a two day period. This was done in patients with mild to moderate congestive failure.
   2. Chronic daily administration of the drug for five weeks. Electrolytes, vital signs and side effects were evaluated at frequent intervals.

Methyclothiazide was found to be an effective diuretic agent causing significant naturesis at optimal dose levels but minimal kaluretic activity at this dose level. Maximal naturetic activity was obtained at a 10 mg. dose while maximal kaluretic activity occurred at a 5 mg. dose level. Although some decrease in serum sodium and chloride levels were noted, no serious derangements of serum electrolytes was observed after a five week chronic study during which time the drug was administered

TABLE IV

BLOOD STUDIES AFTER CHRONIC ADMINISTRATION OF METHYCLOTHIAZIDE (10 mg. daily for 5 weeks)

Pts.	Na. Control 7/20/60	Na. 5 wks.	K Control 7/20/60	K 5 wks.	Cl. Control 7/20/60	Cl. 5 wks.	CO_2 Control 7/20/60	CO_2 5 wks.
1	143	136	4.6	4.1	103	92.5	23.3	24.2
2	148	148	4.3	3.5	103	93	25.8	19.2
3	141	136	4.5	4.3	100	97.5	20.8	22.5
4	142	131	4.3	3.6	103	83.5	22.1	25.8
5	140	130	4.8	4.6	98	87.5	27.5	22.5
6	142	144	4.2	4.4	103	98	20.8	23.3
7	146	144	4.2	4.4	103	98	25.8	23.3
8	146		4.6		103	100	23.3	23.2
9	145	144	5.0	7.9	103	93	30.8	23.3
10	144	135	4.2	3.9	105	95	26.6	25.1
11	147	143	4.4	4.6	100	98	22.1	22.5
12	146	135	4.5	4.2	100	92.5	23.3	24.2
13	144	144	4.6	4.4	100	98	25.8	20.8
14	144		5.0		103		23.3	
15	143	144	4.6	4.4	98	93	22.5	21.6
16	141	142	4.6	4.1	98	90	26.3	24.1
17	144	133	4.0	4.0	100	92.5	26.3	20.4
18	144		3.5		100		27.5	
19	145	141	3.8	3.6	100	90	24.2	25.8
20	145	152	4.5	4.6	100	95	24.2	25.0
21	144	144	4.0	4.2	85	93	24.1	23.2
		4 wks.		4 wks.		4 wks.		4 wks.
22	146	144	4.7	3.5	96	95	17.4	25.8
23	136	140	4.4	3.7	91	87.5	29.2	25

BLOOD STUDIES AFTER CHRONIC ADMINISTRATION OF METHYCLOTHIAZIDE (10 mg. daily for 5 weeks)

Pts.	BUN Control 7/20/60	BUN 5 wks.	Uric Acid Control 7/20/60	Uric Acid 5 wks.	Hct. Control 7/20/60	Hct. 5 wks.	WBC Control 7/20/60	WBC 5 wks.
1	26	30	4.8	4.9	40		4,690	
2	20	20		4.9	47	47	11,600	17,300
3	20	10	4.4	4.7	41	49		
4	17	13	5.6	5.6	39	44	7,480	9,350
5	17	30	4.9	6.9	41		8,460	
6	17	21		5.2	32	42	4,590	11,000
7	17	21	5.3	5.1	48		7,520	
8	20	18			39		6,620	
9	29	37		3.1	32	34	4,950	7,200
10	9	11	5.7		40		4,470	
11	7	12	5.2	5.2	54	55	15,000	12,700
12	14	24	5.4	5.2	34		7,240	
13	14	25	4.8	4.8	43	50	5,470	10,300
14	12		5.2		39	43	4,780	13,200
15	14	17	4.6		33	38	4,600	4,600
16	15	12	5.4	5.2	40	39	12,390	14,300
17	9	14	4.1	5.4	45		7,450	
18	9		3.8		33		5,680	
19	9	14	4.8	4.4	49		9,160	
20	14	17	5.3	5.4	46	42	9,200	10,200
21	13	14		5.3	42	39	7,200	8,800
		4 wks.		4 wks.		4 wks.		4 wks.
22	11	21			40	41	5,600	12,000
23	14	14	4.9	5.1	36	37		

daily. No significant hyperuricemia was noted in any of these 25 patients, although one had a moderate uric acid elevation. Five of these patients had slight BUN elevations. In addition to its potency, methyclothiazide was found to be active continually by maintaining the patients in an edema free state during the chronic study. Significant naturesis above the control output (on a measured NaCl diet) was found over 24 hours after a single 10 mg. dose. In the outpatient study, there was an average weight loss of 3.74 pounds which was effected primarily during the first two weeks of therapy, but was maintained for the balance of the five weeks. After a single 10 mg. dose there was an increase in glomerular filtration rate, in the one "dry" patient in whom this was measured.

None of the patients developed nausea, vomiting or a rash. There was one case of acute gouty arthritis in a non-edematous patient and an unaccountable slight increase in WBC occurred in some patients after chronic administration of the drug. In no case was there elevation of blood glucose.

It is therefore concluded that Enduron is an effective new diuretic agent, with no increased naturetic activity, but the advantages of decreased kaluresis and one of the longest durations of action of any of the thiazide drugs.

REFERENCES

1. Ford, R. V., Moyer, J. H., and Spurr, C. L.: Clinical and laboratory observations on chlorothiazide (Diuril), an orally effective non-mercurial diuretic agent, A.M.A. Arch. Int. Med. 100:582, 1957.

2. Fuchs, M., and Mallin, S. R.: Clinical pharmacology of thiazide derivatives, In, Hahnemann Medical College and Hospital of Philadelphia: Edema, Mechanisms and Management, ed. by J. H. Moyer and M. Fuchs. Philadelphia, Saunders, 1960, p. 276.

3. Novello, F. C., and Sprague, J. M.: Benzothiadiazine dioxides as novel diuretics, J. Am. Chem. Soc. 79:2028, 1957.

4. Fuchs, M., Moyer, J. H., and Newman, B. E.: Human clinical pharamcology of the newer diuretics: Benzothiadiazine and phthalimidine, Ann. New York Acad. Sci. 88:795, 1960.

5. Moyer, J. H., Fuchs, M., Irie, S., and Bodi, T.: Some observations on the pharmacology of hydrochlorothiazide, Am. J. Card. 3:113, 1959.

6. Fuchs, M., Mallin, S. R., Irie, S., Hernando, L., and Moyer, J. H.: A review of the pharmacology and clinical observations of hydrochlorothiazide, A.M.A. Arch. Int. Med. 105:39, 1960.

7. Ford, R. V.: Clinical-pharmacologic investigation of methyclothiazide, a new oral diuretic, Curr. Ther. Res. 2:422, 1960.

8. Fuchs, M.: Therapy of steroid edema. In, Hahnemann Medical College and Hospital of Philadelphia: Inflammation and Diseases of Connective Tissue, ed. by L. C. Mills and J. H. Moyer. Philadelphia, Saunders, 1961, p. 874.

9. Conason, E.: Personal communication.

ADDENDUM*

T. N. JAMES

Dr. Donald R. McCurley of New Orleans has recently told me of studying and treating a patient with both "primary pulmonary hypertension" and adrenocortical insufficiency. The possible relationship of his observations to the findings described in the preceding report are quite apparent, and he has kindly permitted me to describe his case.

A 47 year old married woman with no children complained of fainting spells, fatigue, progressively increasing edema and exertional dyspnea. Prior to the increasing edema she had lost about 40 pounds (130 lbs. to 90 lbs.) in one year, despite a fair appetite. There was no past history of heart disease, murmurs, or rheumatic fever.

Admitting blood pressure was 170/104 but subsequent examinations demonstrated a labile blood pressure which was usually normal. There was brawny pigmentation in areas of dependent edema, but not in the skin creases nor the oral mucosa. Except for rales at both bases, and dependent edema, the remaining significant findings on physical examination were in the heart. The rhythm was regular at 62/min. and cardiac size seemed normal. At the apex there was a grade 2 systolic murmur, poorly transmitted, and also a diastolic rumble with accentuated first mitral sound. The second pulmonic sound was loud and split, and was followed by a blowing diastolic murmur transmitted down the left sternal border.

An electrocardiogram revealed marked right ventricular hypertrophy, with a qR in V1 (R of 10 mm.) and an rS (predominantly S) in V6. On x-ray examination the right ventricle and main pulmonary artery segment were markedly enlarged, with equivocal enlargement of the left ventricle and atrium; the right atrium was moderately enlarged.

At cardiac catheterization a coiled catheter demonstrated a huge right atrium. Pressures in the right ventricle, main pulmonary artery and pulmonary wedge position were, respectively (in mm. Hg), 132/10, 132/55, and 10 (mean). All blood oxygen examinations were normal, and there was no evidence of shunt from either hydrogen-platinum electrode nor cardiogreen dye studies. At the end of the procedure the patient developed paroxysms of nodal premature beats. During an angiocardiogram the next day she became hypotensive (70/40 mm. Hg) but responded promptly to intravenous Wyamine. The angiocardiograms demonstrated a giant right atrium. The final diagnosis was primary pulmonary hypertension with a giant right atrium.

Because of suspected adrenocortical insufficiency, urinary steroid excretion studies were done. Control levels were 2.3 mg. of 17 ketosteroids and 7.0 mg. of 17 hydroxycorticosteroids excretion in 24 hours. The next two days 60 units of ACTH gel was injected intramuscularly each day and urine collected for each of the subsequent 24 hours. Volume of urine the first day was 1120 ml. with 4.2 mg. of 17 ketosteroids and 15.0 mg. of 17 hydroxycorticosteroids. Volume of urine the second day was 1820 ml. with 8.2 mg. of 17 ketosteroids and 26.0 mg. of 17 hydroxycorticosteroids. A diagnosis of moderate adrenocortical insufficiency was made.

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*James, T. N.: Degenerative arteriopathy with pulmonary hypertension: A revised concept of so-called primary pulmonary hypertension, Henry Ford Hosp. M. Bull. 9:271, 1961.

On her discharge from the hospital the digitalis which she had been receiving was discontinued, and 5 mg. of preonisone twice daily was prescribed. On this treatment her appetite improved, she gained 8 lbs. in one month, and had no further edema. Exercise tolerance improved.

If it can be presumed that this patient's adrenal medullary secretions failed at the same time as those from the adrenal cortex, then the postulated contributing role of catecholamines to the pathology of DAPH suggested in the preceding report is strengthened. It would of course be premature to make sweeping conclusions from these preliminary observations, but the clinical events and course of this unusual case fit so well with the morphologic lesions described (especially Case 2) that it was felt they merited description. Dr. McCurley's patient presents but another reason adrenal medullary and cortical function may require more careful evaluation in future cases of degenerative arteriopathy with pulmonary hypertension.

INTERNATIONAL SYMPOSIUM
THE ETIOLOGY OF MYOCARDIAL INFARCTION

NOVEMBER 16, 17, 18, 1961

The professional staff of the Henry Ford Hospital with the advice and support of the Board of Trustees and Dr. Robin C. Buerki, Executive Director of the Henry Ford Hospital, sponsored an international symposium on the subject, The Etiology of Myocardial Infarction. This symposium was held at the Henry Ford Hospital, November 16, 17, and 18, 1961 in the Clinic Auditorium. The program follows and has been prepared with the help of the advisory members:

The Henry Ford Hospital welcomes participants and guests to the Thirteenth in its series of International Symposia in the biological and medical sciences. It is the hope of the Hospital Board and Staff that this meeting will provide new insights into the Etiology of Myocardial Infarction.

Benson Ford
President

Robin C. Buerki
Executive Director

REGISTRATION

3:00 to 10:00 P.M.	Wednesday, November 15, 1961	Terrace Room Foyer of The Statler Hilton Hotel
8:00 A.M. to 12:00	November 16, 1961	The Clinic Lobby of The Henry Ford Hospital

PLACE OF MEETINGS

Scientific Sessions — Auditorium — Henry Ford Hospital

Reception and Dinner — The Statler Hilton Hotel

PROGRAM COMMITTEE

John W. Keyes — Chairman
Detroit

Thomas N. James — Secretary
Detroit

George E. Burch — Advisory Chairman
New Orleans

Herrman L. Blumgart
Boston

Charles K. Friedberg
New York

Robert C. Horn
Detroit

Shirley A. Johnson
Milwaukee

F. Janney Smith
Detroit

William B. Wartman
Chicago

CO-ORDINATOR FOR LOCAL ARRANGEMENTS
David L. Everhart

8:55 Welcoming Remarks — **Robin C. Buerki**

Thursday Morning Session
ENVIRONMENT AND HEREDITY

Chairman George E. Burch
Tulane University
New Orleans, Louisiana

9:00- 9:20	Racial and Ethnic Factors in the Etiology of Myocardial Infarction	**John Yudkin** Queen Elizabeth College *London, England*
9:25- 9:45	Familial and Hereditary Factors in the Etiology of Myocardial Infarction	**Victor A. McKusick** Johns Hopkins Hospital *Baltimore, Maryland*
9:50-10:10	Reasons for Sexual Discrepency in the Incidence of Myocardial Infarction	**William Dock** Downstate Medical Center *Brooklyn, New York*
10:15	General Discussion	

Intermission

Chairman: Herrman L. Blumgart
Harvard Medical School
Boston, Massachusetts

10:40-11:00	Meteorologic Considerations in the Etiology of Myocardial Infarction	**George E. Burch** Tulane University *New Orleans, Louisiana*
11:05-11:25	Phylogenetic Considerations in the Etiology of Myocardial Infarction	**Herbert L. Ratcliffe** Penrose Research Laboratory *Philadelphia Pennsylvania*
11:30-11:45	The Possible Bearing of Voodoo and Other Factors in Primitive Cultures on the Etiology of Myocardial Infarction	**R. J. W. Burrell** Bantu Cancer Registry *Cape Province, South Africa*
11:50-12:15	Germfree Vertebrate Research on the Etiology of Myocardial Infarction: The Role of the Intestinal Flora in Metabolism of Cholesterol, Bile Acid and Vitamin K	**Bengt E. Gustafsson** Karolinska Institutet *Stockholm, Sweden*
12:20	General Discussion	

LUNCHEON

Thursday Afternoon Session
MYOCARDIAL INFARCTION AND MYOCARDIAL NECROSIS

Chairman: Jesse Edwards
Charles T. Miller Hospital
St. Paul, Minnesota

2:00-2:20	Definition of Myocardial Infarction	**William B. Wartman** Northwestern University *Chicago, Illinois*

2:25-2:45	Myocardial Necrosis (With or Without Coronary Occlusion) Induced by Manipulation of Steroids and Electrolytes, and Its Possible Human Analogy	**Hans Selye** University of Montreal *Montreal, Canada*
2:50-3:10	Thrombogenesis, Thrombolysis, Myocardial Necrosis, and Their Relationships to Dietary Manipulations	**Wilbur A. Thomas** Albany Medical College *Albany, New York*
3:15	General Discussion	

Intermission

Chairman: Harper K. Hellems
Seton Hall
Jersey City, New Jersey

3:40-4:00	The Anoxic Heart (Steps in the Metabolic Death of Myocardium Based on Observations from Coronary Sinus Catheterization)	**Richard J. Bing** Wayne State University *Detroit, Michigan*
4:05-4:25	Steps in the Metabolic Death of Myocardium Based on Histochemical and Electron Microscopic Studies	**Robert B. Jennings** Northwestern University *Chicago, Illinois*
4:30-4:50	The Effect of Acute and Chronic Ischemia on Enzymes of the Myocardium	**John S. LaDue** Sloan-Kettering Institute *New York, New York*
4:55	General Discussion	

Friday Morning Session

VASCULAR FACTORS IN CORONARY OCCLUSION

Chairman: William B. Wartman
Northwestern University
Chicago, Illinois

9:00- 9:20	Types of Coronary Obstruction and Their Morphologic Characteristics	**Robert C. Horn** Henry Ford Hospital *Detroit, Michigan*
9:25- 9:45	Coronary Artery Intramural Hemorrhage in the Etiology of Myocardial Infarction	**J. C. Paterson** University of Western Ontario *London, Canada*
9:50-10:10	Inflammatory and Metabolic Changes of the Arterial Wall and Vasa Vasorum, and Their Role in the Pathogenesis of Atherosclerosis and Arterial Occlusion	**William C. Manion** Armed Forces Institute of Pathology *Washington, D. C.*
10:15	General Discussion	

Intermission

Chairman: Robert C. Horn
Henry Ford Hospital
Detroit, Michigan

10:40-11:00	Mast Cells, Endothelium and Thrombosis	**Earl P. Benditt** University of Washington *Seattle, Washington*
11:05-11:25	Thromboplastin Activity of Human Vascular Tissue; Anticoagulant Activity of Vascular Acid Mucopolysaccharides	**John E. Kirk** Washington University *St. Louis, Missouri*
11:30-11:50	Electrochemical Metabolism of the Blood Vessel Wall and Its Possible Relationship to Myocardial Infarction	**Philip N. Sawyer** Downstate Medical Center *New York, New York*
11:55-12:15	Coagulation, Atherosclerosis, and Myocardial Infarction	**Lawson McDonald** Institute of Cardiology *London, England*
12:20	General Discussion	
	LUNCHEON	

Friday Afternoon Session

PATHOLOGIC ANATOMY AND PHYSIOLOGY OF THE CORONARY ARTERIES

Chairman: John W. Keyes
Henry Ford Hospital
Detroit, Michigan

2:00-2:20	Anatomic Factors Influencing the Location of Coronary Occlusion and Development of Collateral Coronary Circulation	**Herrman L. Blumgart** Harvard Medical School *Boston, Massachusetts*
2:25-2:45	Anatomic Relationship of a Coronary Occlusion to the Blood Supply of the Sinus Node and A-V Node in Causing Myocardial Infarction	**Thomas N. James** Henry Ford Hospital *Detroit, Michigan*
2:50-3:10	The Coronary Collateral Circulation in the Etiology of Myocardial Infarction	**Donald E. Gregg** Walter Reed Institute for Research *Washington, D. C.*
3:15-3:35	Vasopressin, Catecholamines and Serotonin as Possible Causes of Myocardial Ischemia	**Timothy J. Regan** Seton Hall *Jersey City, New Jersey*
3:40	General Discussion	
	Intermission	

PATHOLOGIC PHYSIOLOGY OF THE MYOCARDIUM

Chairman: Richard J. Bing
Wayne State University
Detroit, Michigan

4:00-4:30	The Effect of Acute and Chronic Ischemia on Myocardial Contractility	**A. Fleckenstein** University of Freiburg *Freiburg, Germany*

4:35-4:55	The Role of Fats in Myocardial Metabolism and Its Bearing on Both Coronary Occlusion and Myocardial Infarction	**Harper K. Hellems** Seton Hall *Jersey City, New Jersey*
5:00	General Discussion	

Friday Evening

(Statler Hilton Hotel)

6:30 **Reception**

7:30 **Banquet**

Chairman: John W. Keyes

Speaker: R. J. W. Burrell

"Witchcraft, Witch Doctors and Voodoo Death"

Saturday Morning Session

SYSTEMIC FACTORS AFFECTING THE HEART

Chairman: William Dock
Downstate Medical Center
Brooklyn, New York

9:00- 9:20	Physical Effort and the Emotions in the Genesis of Coronary Occlusion and Myocardial Infarction	**Charles K. Friedberg** Mt. Sinai Hospital *New York, New York*
9:25- 9:45	Lipid Mobilizing Factor: Possible Role in Coagulation and Myocardial Infarction	**C. J. D. Zarafonetis** University of Michigan *Ann Arbor, Michigan*
9:50-10:10	Uric Acid Metabolism and Myocardial Infarction	**Charles B. Moore** Ochsner Clinic *New Orleans, Louisiana*
10:15	General Discussion	

Intermission

Chairman: Charles K. Friedberg
Mt. Sinai Hospital
New York, New York

10:40-11:10	Cardiovascular Reflexes and Myocardial Infarction	**Geoffrey Dawes** University of Oxford *Oxford, England*
11:15-11:35	Nicotine in the Etiology of Myocardial Infarction	**Duane G. Wenzel** University of Kansas *Lawrence, Kansas*
11:40-12:00	Cardiovascular Function During Sleep and Hibernation	**Nathaniel Kleitman** *Santa Monica, California*
12:05	General Discussion	

LUNCHEON

Saturday Afternoon Session

COAGULATION

Chairman: Thomas N. James
Henry Ford Hospital
Detroit, Michigan

2:00-2:20	Current Knowledge of Thrombosis and Blood Coagulation	**Shirley A. Johnson** Marquette University *Milwaukee, Wisconsin*
2:25-2:45	Settling of Blood Cell Masses to the Lower Side of Vessels During Life and the Probable Significance	**Melvin H. Knisely** Medical College of South Carolina *Charleston, South Carolina*
2:50-3:10	Determinants of Blood Viscosity	**George O. Clifford** Wayne State University *Detroit, Michigan*
3:15	General Discussion	
	Intermission	

Chairman: Shirley A. Johnson
Marquette University
Milwaukee, Wisconsin

3:40-4:10	Relation of Fibrinolytic Activity to Myocardial Infarction	**Tage Astrup** Carlsberg Foundation *Copenhagen, Denmark*
4:15-4:35	Altered Coagulability of Blood Locally in the Myocardial Microcirculation with Experimental Coronary Occlusion	**Eugene E. Cliffton** Sloan-Kettering Institute *New York, New York*
4:40-5:00	Blood Platelets in the Etiology of Myocardial Infarction	**J. F. Mustard** Sunnybrook Hospital *Toronto, Canada*
5:05	General Discussion	
5:15	Summation of the Symposium	**George E. Burch**

DISCUSSION

In scheduling the program five minutes have been allowed at the end of each presentation to discuss that paper. At the end of each session there will be opportunity for general discussion of all papers presented at that session. Although it is intended that anyone with pertinent remarks be allowed to present them, please confine these within one or at the most two minutes. If this privilege is abused, the chairman of each session is instructed to terminate such remarks. No slides may be shown during the discussion unless cleared with the session chairman prior to the beginning of the session.

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

"PETECHIAL" ANGIOMATA. M. BRANNEN, R. K. NIXON, J. W. DOUCETTE, and R. P. FOSNAUGH. Arch. Derm. 83:386, 1961.

"Petechial" angiomata are acquired capillary tumors which closely simulate true petechiae. These angiomata probably represent forme fruste or early lesions of senile angiomata. There are no regularly associated internal diseases. Increased tortuosity of the scleral vessels is a frequent concomitant finding.

INVESTIGATIONAL VS. PRACTICAL CHEMOTHERAPY. M. BRENNAN, J. Michigan M. Soc. 60:509, 1961.

Medicine will progress if the new is tried. But it must be tried only for serious reasons by seriously interested and experienced students of drug action and toxicity; tried by those who are equipped with an optimum of time, instrumentation, technical and laboratory support in their evaluation task and who will see it as their clear duty to make their observations in an unbiased fashion and to report them thoroughly, promptly, and objectively, to their colleagues through various means created for the exchange of scientific information by professional societies.

TREATMENT OF ADVANCED MAMMARY CANCER WITH 3β, 17β — ANDROSTANEDIOL. M. J. BRENNAN, V. L. BECKETT, J. E. KELLY, and G. BETANZOS. Cancer 13:1195, 1960.

3β,17β-Androstanediol is effective in the suppression of advanced breast cancer in postmenopausal women. How it actually compares with testosterone propionate will have to await more extensive studies. In this double-blind study, 3 regressions occurred in 21 patients on androstanediol, and 2 regressions occurred in 23 patients on testosterone. Androstanediol appears to be less masculinizing than does testosterone propionate.

PREDUODENAL PORTAL VEIN CAUSING DUODENAL OBSTRUCTION ASSOCIATED WITH PNEUMATOSIS CYSTOIDES INTESTINALIS. M. A. BLOCK and E. A. ZIKRIA. Ann. Surg. 153:407, 1961.

Obstruction of the duodenum is rarely caused by a portal vein passing anterior to the duodenum. A patient with this condition in whom the duodenal obstruction was relieved by a duodeno-duodenostomy is recorded. Pneumatosis cystoides intestinalis of the lower ileum was also present in this patient and disappeared following relief of the duodenal obstruction.

RESPIRATORY SYMPTOMS AND VENTILATORY FUNCTION IN 172 ADULTS EMPLOYED IN A BANK. G. BOWER. Amer. Rev. Resp. Dis. 83:684, 1961.

A survey to detect chronic bronchitis and asthma-like conditions is reported. One-hundred and seventy-two adult men and women more than 40 years old, employed in a bank, were questioned regarding respiratory symptoms. Spirograms were obtained, and the maximal midexpiratory flow was computed for each subject. Forty-two persons (roughly 24 per cent of the total) had respiratory symptoms suggesting the likelihood of chronic pulmonary disease. Ventilatory function in 27 of these persons was not impaired. In 15 persons, there was evidence of impaired ventilatory function. Men with chronic cough and expectoration had a significantly lower mean maximal midexpiratory flow than men without cough and expectoration. Prolonged cigarette smoking was closely associated with chronic cough and expectoration. Ventilatory function in male non-smokers was significantly better than in smokers; no significant difference in ventilatory function was found between women non-smokers and smokers.

PORPHYRIA, DIABETES, AND THEIR RELATIONSHIP. T. K. BURNHAM and R. P. FOSNAUGH. Arch. Derm. 83:717, 1961.

The association of diabetes mellitus with porphyria, first reported in 1949, has since been noted by several authors, as has the associated disturbance of iron metabolism and hemochromatosis. It would seem that the metabolic defect of porphyria may actually result in the development of diabetes mellitus due to the disturbance of iron and pyrrole metabolism. A patient with porphyria cutanea tarda is reported in whom diabetes mellitus developed 4 years after the onset of cutaneous symptoms. The striking bluish-gray tint of the skin and increased iron in the bone marrow were thought to represent early hemochromatosis. The nature of the enzymatic blocks in the different forms of porphyria, their method of action, and the rationale of chelation therapy are discussed. A case report in which chelation resulted in striking improvement of liver function is quoted. It is suggested that chelation may also reverse diabetes mellitus secondary to the disturbance of porphyrin metabolism when the latter is corrected. We plan to treat our patient with chelation in an attempt to control both his porphyria and diabetes.

POTENT HYPOTENSIVE DRUGS: COMPARATIVE ANALYSIS OF A GANGLIONIC BLOCKING AGENT AND TWO NEW SYMPATHETIC INHIBITORS IN SEVERE HYPERTENSION. J. R. CALDWELL, G. LAUBINGER, and K. P. SCHMIDT. J. Michigan M. Soc. 60:352, 1961.

Despite various clinical successes with the rauwolfia's, thiazides and hydralazine as antihypertensive agents, treating the more severe forms of hypertension still remains a difficult problem. A malignant hypertension or hypertension with complications (cardiac insufficiency, azotemia, papilledema, and the like) particularly, are often unresponsive to these agents. Although these forms of hypertension have responded to the ganglionic blocking agents of which mecamylamine (Inversine®) is most representative, the severity of side reactions to these agents — constipation, blurring of vision, etc. — limits their therapeutic usefulness. Recently reference to two

new antihypertensive agents which may replace the ganglionic blockers for the more severe forms of hypertension appeared almost simultaneously in the clinical literature. One of them was bretylium tosylate (Darenthin) and the other was guanethidine (Ismelin). As a result of our study we conclude that guanethidine demonstrates definite superiority over the other two agents — both from the point of view of therapeutic effectiveness and in the important area of lessened or innocuous side effects.

RELIEF CHAMBERS IN COMPLETE DENTURES. R. L. CAMPBELL. J. Pros. Den. 11:230, 1961.

A survey of the status of the use of relief chambers in the construction of complete upper dentures was made by a review of the literature and by a questionnaire returned by the prosthetic departments of fifty-three dental schools. The results indicate that opinions and practices are widely variable, that the question is an open one with many ramifications, and that the basis for much of what is done is in need of further study and appraisal.

POSTOPERATIVE MYELOGRAPHY. H. P. DOUB, AND J. E. SHICK. West J. Surg. 69:185, 1961.

A study was made of 85 patients who had postoperative myelograms and a second operation. These represented 6.9% of all positive myelograms studied. The time interval between operations varied from a few weeks to 13 years. A correct preoperative diagnosis was rendered in 71 cases, or 83.5%, before second operation. In 9 cases scarring, with or without bony overgrowth, was found at operation. The remaining 5 represented single cases of various types, and thus 14 were incorrectly diagnosed. Following the second operation 35 patients diagnosed were asymptomatic, 23 were improved, 22 were not improved, and 5 had no follow-up.

RESTORATION OF INTESTINAL CONTINUITY AFTER SUBTOTAL COLECTOMY FOR ULCERATIVE COLITIS. L. S. FALLIS, J. BARRON, and E. CAMACHO. West. J. Surg. 69:148, 1961.

The concept of utilizing a diseased portion of the intestinal tract for anastomotic purposes is so contrary to generally accepted surgical principles that many surgeons are loathe even to consider the operation. However, a reevaluation of the problem appears to be indicated when it can be shown that the operation can be performed without unduly jeopardizing the patient's life or the opportunity for restoration to a satisfactory condition of health. The follow-up period of this series is much too short to formulate any conclusions regarding the two really important questions, viz., what is the chance of a serious exacerbation in the retained rectal segment; and what is the hazard of carcinoma? Abel, with an extensive experience of over 200 ileo-rectostomies, states that carcinoma has developed in only 2 patients, an incidence of 1.0%. These potential dangers are indicative of the necessity for keeping these patients under continuous surveillance. All that can be said at the present time is that the operation is feasible and that the vast majority of patients are extremely grateful for having deferred, at least temporarily, the unpleasant features of an artificial anus.

***CONTINUOUS METABOLIC STUDIES ON NORMAL AND DEPANCREATIZED DOGS DURING REPEATED WHOLE BODY X IRRADIATION.** O. H. GAEBLER, R. J. BLOOR, and H. C. CHOITZ. Canad. J. Biochem. 39:863, 1961.

Experiments on normal and depancreatized bitches were carried out to determine how well multiple doses of 90 r or less of X radiation are tolerated, and whether there are any metabolic effects suggesting stimulation or suppression of the adrenals. In two normal animals, total dosage for the main portion of the trunk was 574 and 3549 r, in 4 and 22 months, respectively; in the depancreatized one, 807 r in 9 months. Dosages for head and pelvis approximated 44% of these amounts. Food intake was constant, and daily records were kept of body weight, water intake, urine volume, and urine nitrogen. The general condition of all animals remained excellent. Periods of estrus continued. Weight was maintained or increased during long series of exposures. No changes in water balance or nitrogen output occurred which resembled those observed in dogs receiving corticotropin or hydrocortisone. In the depancreatized animal, the insulin requirement, known for 5 preceding years, was unaffected. Thus no evidence for stimulation or suppression of adrenal function was obtained. Histological examination of bone marrow and other tissues of the animal which received the largest total dose gave little evidence of damage. Moderate increases in urine volume of the normal animals suggested possible early renal impairment.

SOME BACTERIOLOGICAL DATA ON DERMATOLOGICAL PATIENTS. 1. ANTIBIOGRAMS AND PHAGE TYPES OF STAPHYLOCOCCI. J. E. GREER, R. R. MENARD, and C. S. LIVINGOOD. J. Invest. Derm. 36:273, 1961.

Despite many studies on staphylococcal infections in the surgical patient, the medical patient, and the infant, there is a dearth of bacteriological data on dermatological patients, especially in-patients. This paper presents representative bacteriological data on some of the out-patients and in-patients treated in this department during the period 1955-1960. The antibiograms and phage types of strains of *Staphylococcus aureus* are listed and correlated with the diagnoses of the patients and sites from which the strains were isolated. Of 2545 different strains from 2016 patients, about 60% were resistant to penicillin, with about 30% resistant to penicillin only. Approximately 20% were resistant to tetracycline; more than half of these were resistant to streptomycin as well. No increase in the percentage of antibiotic resistant strains isolated annually was observed.

DARIER'S DISEASE: REPORT OF A CASE COMPLICATED BY KAPOSI'S VARICELLIFORM ERUPTION. J. F. HITSELBERGER, and R. E. BURNS. Arch. Derm. 83:425, 1961.

A case of Kaposi's varicelliform eruption in a patient with Darier's disease is reported. Darier's disease is regarded as fundamentally a dyskeratosis rather than an eczematous dermatosis, and is transmitted as a simple dominant characteristic. This followed contact with labial herpes simplex. The Darier's disease cleared slowly following the episode of Kaposi's eruption and treatment with high doses of vitamin A.

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STUDIES ON ALBINISM: THE DEMONSTRATION OF DOPA-POSITIVE MELANOCYTES IN ALBINO SKIN. F. HU, R. P. FOSNAUGH, and P. F. LESNEY. Arch. Derm. 83:723, 1961.

In a previous paper we have reported the results of silver and dopa reactions performed on normal and vitiliginous skins. It seems pertinent to do similar studies on the skins of patients suffering from incomplete generalized albinism. Incidental to these studies, which entailed exposing our subjects to progressively increasing doses of ultraviolet light, we were able to observe these patients during their change in capacity to tolerate sunlight. Our study indicates that: The melanocytes are present in normal numbers and distribution in the skins of albinos and are dopa-positive. They appear to be activated by ultraviolet light irradiation. The enzyme, tyrosinase, is present in the albino melanocytes but is possibly in an inhibited form. It is possible that there is, in addition, a block of pigment transfer from the albino melanocytes to the epithelial cells of the epidermis. Methoxsalen appears to be effective in increasing skin tolerance to sunlight in albinos, although it does not result in tanning.

DERMATOLOGY. C. S. LIVINGOOD. In, GARLAND, J., and STOKES, J. III, eds.: The Choice of a Medical Career: Essays on the Fields of Medicine, Philadelphia, Lippincott, 1961.

We know from the earliest medical writings, about 3500 years ago, that cutaneous diseases have always constituted one of the major interests of medicine. Three dermatological textbooks were published before 1850 in Europe, and one in the United States. For many years dermatology included syphilology, and leading contributions were made to these fields by the investigators Schaudinn, Wassermann, and Ehrlich. The evolutionary development of dermatology, from the morphologic and classification era to the present functional era, has been accompanied by the emergence of the specialty as a clinical science. Allergic mechanisms of cutaneous disease make it evident that the specialty has an important stake in the field of allergy and immunology, as partially illustrated by epidermal sensitization, local and general sensitivity, cross sensitization, atopy, drug allergy, and serum and cell antibodies.

Of late years there has been an unparalleled surge of interest in cutaneous physiology and biochemistry of the skin, leading to the concept of enzymatic basis for itching, evaluation of sweat retention, elucidation of pigment metabolism, and other advances too numerous to be mentioned. The diseases of the skin represent 8 to 12 percent of the practice of medicine. Dermatology is an increasing challenge, an unlimited and continuing opportunity and offers the fellowship of lifelong enthusiasts.

PYOGENIC DERMATOSES. C. S. LIVINGOOD and J. B. KOPSTEIN. In, Noojin, R. O., ed.: Dermatology for Students, Springfield, C. C. THOMAS, 1961, p. 246.

It is probable that cutaneous bacterial infections account for more disability than any other single group of skin diseases. The importance of learning to recognize the classic signs of bacterial invasion of the skin and mastering the fundamental principles of management of such infections is obvious because each day almost

every practicing physician will see several patients in this category. In recent years the increase of both cutaneous and systemic infections due to antibiotic resistant staphylocci, especially in hospitalized patients, has compounded the problem.

The management depends on classification of pyoderma, bacteriology, predisposing factors, and proper use of antibiotics. Some of the most severe primary problems are impetigo, ecthyma, deep folliculilis paronychia and erysipelas. Skin damage either by disease or traum is subject to secondary bacterial infection, usually coagulase-positive staphylococci, beta hemolytic streptococci or both. It is important to recognize the pre-existing skin disease such as scabies, contact dermatitis, or similar conditions. Suppurative hidradenitis may be a very severe disorder of the axillae, groins or perianal region, calling for surgical treatment of the deep seated nodules.

DENTAL ABSCESS WITH SINUS TRACT FORMATION. C. F. A. McCluer, Jr., and R. E. Burns. Arch Derm. 83:941, 1961.

In the differential diagnosis of certain facial and parafacial lesions, it is well to consider the possibility of dental abscess with the formation of a sinus tract to the skin. A cutaneous lesion of granulomatous or, less often, neoplastic appearance, occasionally exuding serous or purulent material and involving the inner canthus of the eye, the nasolabial fold, the chin, neck, or adjacent area, should be regarded as a possible exit point for a draining, chronic dental abscess. Occasionally the abscess may point beneath the skin and appear as a fluctuant cystic swelling which might well be mistaken for a boil or a carbuncle or for an infected epithelial cyst, a dermoid cyst, a branchial cleft or thyroglossal duct cyst, a parotid fistula, or even a tuberculous or deep mycotic infection. The combination of dental abscess and fistula tract formation to the skin is a syndrome often misdiagnosed. Three such cases were noted within a year's time.

QUINIDINE INTOXICATION TREATED BY ISOPROTERENOL (ISUPREL). S. N. Nickel, and Y. Thibaudeau. Canad. Med. Ass. J. 85:81, 1961.

A case of ventricular flutter due to quinidine, successfully treated by isoproterenol, is reported. A review of the literature on quinidine intoxication failed to reveal any patient previously treated by this drug. Because of the theoretical reasons discussed, and because of the ease of administration of isoproterenol, we believe this drug to be the best antidote available at present for the treatment of cardiac arrhythmias due to quinidine. In the future its ready availability at the patient's bedside could be a life-saving measure.

THE CONTRIBUTION OF PERORAL MUCOSAL BIOPSY TO THE DIAGNOSIS OF GASTROINTESTINAL DISEASE. W. G. O'Driscoll and W. S. Haubrich. J. Mich. Med. Soc. 60:500, 1961.

Eighty peroral mucosal biopsies of the stomach and small intestine were attempted employing the Crosby capsule. Tissue was obtained in seventy-one attempts (89 per cent). The specimens were adequate for histologic examination and diagnosis in all

but four instances. The diagnostic contribution of these biopsies in a variety of conditions is discussed. Peroral biopsy is most useful in the diagnosis of diffuse disease of the gastric or intestinal mucosa. The discomfort to the patient is minimal, and we have encountered no untoward complication of the procedure.

PULMONARY VEINS IN CONGENITAL HEART DISEASE IN THE ADULT. R. S. ORMOND, A. K. POZNANSKI, and A. W. TEMPLETON. Radiology, 76:885, 1961.

Pulmonary veins in congenital heart disease reflect the flow of blood through the lung fields. In those conditions which lead to an increase in flow, the veins are large. In lesions such as pulmonary stenosis and pulmonary hypertension, leading to shunt balance and reversal, in which the cardiac output is reduced, the veins are small. In patent ductus arteriosus, evaluation of the state of the pulmonary physiology can be made by comparing the size of the veins with the size and configuration of the arteries. In patients with pulmonary hypertension, a successful surgical result depends upon the presence of a significant left-to-right shunt. Vein size offers one more method of evaluating the amount of such a shunt.

*AN AUTO-RECORDING MECHANISM FOR ASSAY OF ULTRA-THIN RADIOACTIVE, VACUUM CONDENSED FILMS. L. E. PREUSS AND C. BUGENIS, Transactions of the Seventh National Symposium on Vacuum Technology, 1960. New York, Pergamon Press, 1961, p. 260.

An automated device for continuous recording of vacuum condensed, pile-produced metal radio-nuclide surface concentrations, down to 10^{-11} g/cm², has been designed using scintillation counters for α, β, or γ detection. Continuous or interrupted condensates, scanned through special collimators, are driven by a variable speed transport mechanism. A chart indexing system locates the point of assay on the film. Film thickness is determined either by gravimetric or chemical calibrations on the device itself. Best resolution is for particulate emission and is reduced for photons, due to gamma leakage through the collimators. 5 mm strips at about 14×10^{-3} mc total activity are resolved at 0.5 mm edge-to-edge separation, using a 2 mm "square" aperture, with Au^{198} gammas. The same strips at about 9×10^{-3} mc activity are resolved for Au^{198} betas at 0.25 mm separation, using a 1 mm "V"-type aperture. 1 mm regions at 1 mm separation are resolved for Au^{198} betas or gammas of activity between 10^{-3} and 10^{-4} mc. Ratio of recorder peak output to specimen activity is nearly linear; at 98 per cent and 96 per cent for particulate and photon emission respectively.

*THE SPECTRA OF SOME BETA-EXCITED X-RAY SOURCES WITH THE MULTICHANNEL ANALYZER. L. E. PREUSS, H. HORN, and T. W. KEISER. Adv. X-Ray Analysis 4:280, 1961.

Three beta-excited X-ray source types (the compound, apposition, and mixture source) have been designed, and the photon spectra compared. Each source in a

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series was assembled using a single target element with the concentration of pure beta emitter held constant for the series. The apposition source was studied with varying target thicknesses. The compound sources were crystalline precipitates of molybdate and tungstate groups compounded with the noncarrier-free beta emitter. The mixture source consisted of a fine-milled target powder with the beta emitter adsorbed on it. Assay of the x-ray source emission has been done on the Radiation Instrument Development Laboratories (RIDL) 100-channel analyzer with a 3-in. Nal detector. Variation in the spectra exists between the source types of a series. Anomalous peaking occurs with the Sr^{90} MoO_4 source emission at 29 kev. The compound source, potentially productive, demonstrates poor characteristic spectra.

SUBACUTE BACTERIAL ENDOCARDITIS: CLINICAL AND LABORATORY OBSERVATIONS IN 27 CONSECUTIVE CASES TREATED WITH PENICILLIN V BY MOUTH. E. L. QUINN and J. M. COLVILLE. New England J. Med. 264:835, 1961.

Definite bacteriologic cure was achieved in 21 (77.8 per cent), and probable bacteriologic cure in an additional 3 (11.1 per cent), a total of 24 (88.8 per cent) definitely or probably cured. Bacteriologic failure was observed in 3 patients (11.1 per cent); however, 2 died of an associated condition before the planned therapy was completed. Oral administration of 7.2 gm. of penicillin per twenty-four hours for prolonged periods was well tolerated. Penicillin V, 1200 mg., administered orally every four hours, produced penicillin serum concentrations comparable to those achieved with 600,000 units of aqueous procaine penicillin G given intramuscularly every six hours. One of the 27 patients failed to absorb "adequate" amounts of penicillin from the gastrointestinal tract, and in this patient bacteriologic relapse occurred. Thus, oral penicillin therapy of bacterial endocarditis requires monitoring of the adequacy of intestinal absorption of penicillin by determination of serum concentration or serum inhibitory activity in *each* patient. With this limitation, the oral route may be substituted for the parenteral in the various therapeutic regimens advocated as successful for treatment of this disease.

*STUDIES ON THE MITOCHONDRIAL A-GLYCEROPHOSPHATE DEHYDROGENASE. II. EXTRACTION AND PARTIAL PURIFICATION OF THE DEHYDROGENASE FROM PIG BRAIN. R. L. RINGLER. J. Biol. Chem. 236:1192, 1961.

The extraction of *a*-glycerophosphate dehydrogenase in soluble form with the aid of phospholipase A from acetone powders of pig and sheep brain and of beef skeletal muscle mitochondria has been described. All snake venoms known to be good sources of phospholipase A liberated the dehydrogenase in soluble form, whereas phospholipases C and D as well as a general lipase from wheat germ were completely ineffective. An inactivation, which amounts to about 50% in the phenazine methosulfate assay routinely used, accompanies the release of the dehydrogenase. Both the inactivation and the liberation of the enzyme from the particle appear to be the result

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of the action of phospholipase A. A procedure for the partial purification of the enzyme from pig brain mitochondria was described. The purified preparation appeared to be homogeneous in electrophoresis but heterodisperse in the ultracentrifuge. Chromatography on hydroxylapatite columns resulted in several enzymatically active peaks. The purified enzyme ($Q_{O_2} = 2600$) was found to contain non-heme iron (1 mole per 3.5×10^5 g of protein) and flavin (1 mole per 2.1×10^6 g of protein) as the only recognizable metal or vitamin constituents.

CLINICAL REPORT ON METHAMINODIAZEPOXIDE (LIBRIUM). R. R. SCHOPBACH. Amer. J. Psychiat. 117:923, 1961.

Methaminodiazepoxide (Librium) was beneficial for 60% of obsessive compulsive patients and for about one-third of others suffering from chronic neuroses and/or depression. These benefits achieved by patients previously considered therapeutically unpromising indicate that this drug is a valuable addition to our armamentarium. In the dosage of 10 mgm. q.i.d. side effects were minimal.

NEUROANATOMICAL CORRELATES OF AUDITORY SENSITIVITY AND PITCH DISCRIMINATION IN THE CAT. H. F. SCHUKNECHT. In, RASMUSSEN, G. L., and WINDLE, W., eds.: Neural mechanisms of the auditory and vestibular systems. Sprinkfield, C. C. THOMAS, 1961.

The neural coding system for pitch perception has been a concern of neurophysiologists for some time. The brilliant investigations of such men as Wever, Davis, von Békésy, Tasaki, Galambos, and others, have gone far in describing the physical and neural events occurring during the reception and transmission of auditory information. It is probably correct to say that most of those who have applied themselves in some way to problems relating to pitch perception have accepted as a working hypothesis the concept that pitch coding is based on both the frequency and the spatial patterning of neural impulses, with frequency being more important for low tones and place of maximal stimulation along the receptor organ being more important for high tones.

The purpose of this paper is to examine the neuroanatomical sturctures and physiological mechanisms of the coachlea and attempt to correlate them with psychophysical measurements of hearing. All of the data is taken from experiments on cats performed during the past ten years. The methods used to spatially orient sensory and neural units in the cochlea by graphic reconstruction, as well as the techniques for behaviorally conditioning cats for pure-tone thresholds and for pitch discrimination, have been described elsewhere. Reports follow under the following headings: Frequency Localization on the Organ of Corti and Spiral Ganglion, Threshold Sensitivity and Pitch Discrimination in the Cat, Localization and Spread of Fields of Excitation in the Cat, Cochlea as a Function of Frequency and Intensity, Hair Cell and Ganglion Cell Populations and Auditory Thresholds, and Weber Fraction Cell Populations and Frequency Distribution.

STUDIES OF ARTHRITIS AND OTHER LESIONS INDUCED IN RATS BY INJECTION OF MYCOBACTERIAL ADJUVANT. IV. EXAMINATION OF TISSUES AND FLUIDS FOR INFECTIOUS AGENTS. J. T. SHARP, B. H. WAKSMAN, C. M. PEARSON, and S. MADOFF. Arthritis & Rheum. 4:169, 1961.

Adjuvant induced arthitis is believed to be due to an immunological process associated with the development of delayed hypersensitivity to a component of the injected mycobacterial adjuvant. However, since pleuropneumonia-like organisms (PPLO) may cause arthritis in rats, it was necessary to determine whether such microorganisms play any role in adjuvant disease. This article reports attempts to cultivate bacteria and PPLO from affected tissues and to transfer disease to normal recipients. No evidence for an infectious agent was obtained.

COMMON RHEUMATIC DISORDERS. PART II: RHEUMATOID ARTHRITIS. J. W. SIGLER and D. C. ENSIGN. Amer. Practit. 12:327, 1961.

Rheumatoid arthritis is a clinical diagnosis applicable to a fairly consistent pattern of symptoms and signs. It constitutes a segment in the broad spectrum of the diseases of connective tissue. While the etiology is unknown and hence no "cure" is available, certain empiric principles of treatment have been found to be of value. As a working rule, the earlier the diagnosis is made and the earlier comprehensive therapy is instituted, the better will be the outcome in the individual patient. We have attempted to alert the practitioner to the early manifestations of this disease and to suggest a therapeutic approach which emphasizes measures of proved value.

USE OF NERVE BLOCK ANESTHESIA IN SURGERY OF THE HAND. S. STANISAVLJEVIC. Arch. Ortop. (Milano) 73:918, 1960.

The author has emphasized some of the principles which are important in the administration of nerve block anesthesia. To know the anatomy of nerve distribution and the exact region which is to be operated upon is most important. For example, closed or open reduction and internal fixation of fractures of the meta-carpal bones always require ulnar nerve anesthesia (because of the attachment of the interosseus muscles). The pneumatic tourniquet was always used with nerve block anesthesia. The tourniquet was very well tolerated by the patients for 30-45 minutes, after which time it had to be released for 5 minutes and reapplied. The author in a few cases reapplied the tourniquet 3 times with no discomfort to the patient. The author believes that nerve block anesthesia is safe for the patient and a satisfactory type of anesthesia for use by the surgeon.

THE SIGNIFICANCE OF ATRIAL FIBRILLATION. R. E. TABER and C. R. LAM. Minnesota Med. 44:148, 1961.

The results attained in 426 mitral commissurotomy patients who have been followed from 2 to 8 years have been summarized. The short and long term results were observed to be significantly different depending on whether atrial fibrillation was present. In an attempt to clarify the indications for open mitral commissurotomy

in mitral stenosis, those patients with a high operative and late mortality as well as poor late functional results have been further studied. Two-hundred (43 percent) of the 426 patients had developed atrial fibrillation by the time of commissurotomy. This group of patients received the most unsatisfactory results, largely due to fatalities occurring from arterial embolization. The results of 34 open operations on the mitral valve are presented. Thirteen of these procedures were carried out for pure mitral stenosis and four for combined stenosis and insufficiency. The indications for open surgery in the patients with pure stenosis were: previous embolic disease in 4 cases and restenosis in 9. Examples of each type are given. The high operative mortality and poorer late results attained with the closed operation in all patients with atrial fibrillation indicate that this finding is probably sufficient indication for open mitral commissurotomy.

PROLONGED INTRA-ARTERIAL CHEMOTHERAPY FOR INOPERABLE CANCER: A TECHNIQUE. J. L. TUCKER, JR. and R. W. TALLEY. Cancer 14:493, 1961.

New concepts in chemotherapy for inoperable cancers include the use of antimetabolites that by the mechanism of their action necessitate prolonged intra-arterial infusion. A simple method using an inexpensive pump for these intra-arterial infusions is described. The method and pump are particularly useful because of their practicality, dependability, and mechanical simplicity. This technique can easily be applied to prolonged intra-arterial drug administration for other purposes.

INTRA-ABDOMINAL COLOR PHOTOGRAPHY (PHOTOLAPAROSCOPY). G. A. UHLICH and E. G. MERRITT. Amer. J. Dig. Dis. 6:322, 1961.

The method of exploring the abdomen by endoscope, developed early in the century by Kelling and by Jacobaeus, today represents a valuable diagnostic procedure. Objective documentation of laparoscopic findings in a simple and safe way has become possible by the use of modern equipment. Results obtained with a Sass-Wolf photolaparoscope have been discussed and illustrated by 12 color reproductions of intra-abdominal views.

AORTO-ESOPHAGEAL FISTULA: AN UNUSUAL COMPLICATION OF ESOPHAGO-GASTROSTOMY, FOLLOWING RESECTION OF CARCINOMA OF THE ESOPHAGUS. A. S. ULLMANN, K. J. SHIER, and R. C. HORN, JR. Canad. Med. Ass. J. 85:27, 1961.

A case of aorto-esophageal fistula is reported resulting in the death of the patient, who previously underwent esophago-gastrostomy for carcinoma of the esophagus. Primary peptic ulcer, due to the digestive effect of gastric juice at a site of lessened resistance, and secondary invasion by yeast-like organisms as a contributory factor, are proposed as causes of this unusual complication of esophago-gastrostomy.

CHEMOTHERAPY OF ADVANCED OVARIAN CANCER. V. K. VAITKEVICIUS, R. W. TALLEY, M. J. BRENNAN and J. E. KELLY. J. Mich. Med. Soc. 60:492, 1961.

Ovarian carcinoma has an unpredictable course and, despite dissemination of the disease, long-term survivals without therapy occur. Only when actively progressive and symptomatic disease is present is systemic chemotherapy indicated. Effective palliation of symptoms and possibly also some prolongation of life is possible in approximately one-third to one-half of the patients with advanced ovarian cancer. Chlorambucil and cyclophosphamide appear to be, presently, the drugs of choice in chemotherapy of ovarian cancer because of their relative safety and ease of oral administration, rather than any greater efficacy. Cross-resistance seems to be present between different radiomimetic drugs. Therapy with drugs with different mechanisms of action (such as 5-fluorouracil and Vincaleukoblastine) sometimes are effective in radiomimetic resistant patients.

*MANIFESTATIONS OF WHIPPLE'S DISEASE IN THE HUMAN SMALL INTESTINE MUCOSA. J. H. L. WATSON, and W. S. HAUBRICH. Proc. European Regional Conference on Electron Microscopy, Delft 1960, 2:921, 1960.

Whipple in his original description of the disease, mentioned abnormal non-lipid in the intestinal mucosa and mesenteric lymph nodes, but later observers emphasized the fatty accumulations and neglected the less obvious non-lipid abnormalities. In the present report attention is redirected toward the non-lipid substance. With attention focussed on the ubiquitous SPC cells and their PAS-positive contents the question arises as to the relationship between these cells and the PCC with which they are associated. The majority of the evidence supports a conclusion that the PAS-positive substance, including the sickle-form particles, occur in the SPC cells as a result of cytoplasmic elaboration. It seems feasible that in the intestine of Whipple's disease the presence of an abundant, abnormal protein-carbohydrate material and its effect on the fine vascular structures may be primarily responsible for the impaired intestinal absorption, which often attends Whipple's disease. Although the apparently normal ultrastructure of the intestinal epithelial cells in our 3 cases by no means excludes a functional defect, the facts that these epithelial cells are morphologically intact and that none of the abnormal material has been observed within these cells lend credence to the suggestion that the absorptive defect in Whipple's disease lies with the lamina propria rather than in the epithelium. From the general appearance of the vacuolated, cylindrical bodies in electron micrographs, and from the suggestion of their having at least some sort of internal organization, one must also theorize that the bodies could be of the nature of bacteria within the lamina propria. In this event the SPC cells of the disease could be carrying out some phagocytizing function. Certainly, a complete understanding of this fascinating disease is only beginning.

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***A STUDY OF TACTOID-FORMING CRYSTALS OF β-FeOOH. J. H. WATSON, W. HELLER, and T. SCHUSTER. Proc. European Regional Conference on Electron Microscopy, Delft, 1960, 1:229, 1960.**

As part of a wider investigation of tactoids, it becomes desirable to determine the dimensions and structure of tactoids of β-FeOOH and of the microcrystals composing them. The crystals were prepared by a slow hydrolysis of a variety of controlled solution concentrations of $FeCl_3$. Particle distribution measurements showed that the mean length of the crystals decreased with initial $FeCl_3$ concentration. There was evidence from the plot of concentrations versus axial ratios for simultaneous growth changes in all three axial directions. Methods of shadow casting indicated that the microcrystals might be square on cross section. Ultrathin sectioning of the crystals for electron microscopy supported this conclusion and showed that the crystals were present in cubic packing. Both longitudinal and cross sections showed a laminar structure within the microcrystals. The structural dimensions were the order of 35 Angstrom units. X-ray diffraction analysis showed the same pattern for β-FeOOH whether mounted on a dry powder or within the embedding material for sectioning.

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